

Editors: Berek, Jonathan S.

Title: *Berek & Novak's Gynecology, 14th Edition*

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Preface

The 1st edition of *Novak's Textbook of Gynecology* appeared in 1941, written by the distinguished Dr. Emil Novak of Johns Hopkins. The book became a successful and important international reference for the practice of gynecology. When I undertook the extensive expansion and reorganization for the 12th edition in 1995, it was a great honor to be invited to become the editor, and it is my privilege to continue in this role for the 14th edition, which bears the title *Berek & Novak's Gynecology*.

The book retains the format of the prior two editions, enhanced by full color illustrations and photographic reproductions. As with the previous editions, the goal is to provide a comprehensive summary of the specialty of gynecology. All chapters have been thoroughly revised to provide timely information and references. Special attention has been paid to the illustrations and photographs to make them more accessible and informative. A new section on "Urogynecology and Pelvic Reconstructive Surgery," with chapters devoted to urogynecology, prolapse and colorectal problems, has been added to address the new subspecialty and our expanded role as gynecologists in this essential area of care. The increasing use of nontraditional medicine in gynecology inspired the inclusion of a chapter on Complementary Medicine.

This textbook, originated by the faculty of the Johns Hopkins University School of Medicine, continues to reflect the contributions of that great institution. After the 5th edition and subsequent death of Dr. Novak in 1957, many physicians from Johns Hopkins, and subsequently some members of the Vanderbilt faculty, helped carry the torch—Dr. Edmund R. Novak through the 9th edition in 1979; Drs. Howard W. Jones, Jr. and Georgeanna Seegar Jones through the 10th edition in 1981; and Drs. Howard W. Jones,

III, Lonnie S. Burnett, and Anne Colston Wentz through the 11th edition in 1988. These editors, assisted by many contributors from the faculty at Johns Hopkins, especially Drs. J. Donald Woodruff and Conrad G. Julian, helped define the specialty of gynecology during the latter half of the 20th century. These physicians shaped the practice of gynecology as we know it today—its surgical and medical therapies, reproductive endocrinology, assisted reproductive technologies, gynecologic oncology, urogynecology, and infectious diseases. As a graduate of Johns Hopkins University School of Medicine, I am proud to contribute to that rich tradition.

Berek & Novak's Gynecology, 14th edition, is presented in eight sections. The first, "Principles of Practice," includes the initial assessment of the gynecologic patient, the history and physical examination, and communication skills. This section addresses ethical principles of patient care, quality assessment and improvement, and the epidemiology of gynecologic conditions. The second section, "Basic Principles," summarizes the scientific basis for the specialty—anatomy and embryology, molecular biology and genetics, and reproductive physiology. The third section, "Preventive and Primary Care," emphasizes the importance of primary health care for women, which has evolved to address preventive care, screening, family planning, sexuality, and common psychiatric problems. The fourth section, "General Gynecology," reviews benign diseases of the female reproductive tract, the evaluation of pelvic infections, pain, intraepithelial diseases, the management of early pregnancy loss and ectopic pregnancy, and the evaluation of benign breast disease. The fifth section, "Operative General Gynecology" covers perioperative care, and the operative management of benign gynecologic conditions using endoscopy and hysterectomy. The sixth section is new—"Urogynecology and Pelvic Reconstructive Surgery." The seventh section, "Reproductive Endocrinology," summarizes the major disorders affecting the growth, development, and function of women from puberty through menopause. The eighth section, "Gynecologic Oncology," covers malignant diseases of the female reproductive tract and breast cancer.

I acknowledge the many individuals who contributed to this book. I am grateful to Rebecca Rinehart for her superb editorial assistance and to Tim Hengst, an outstanding medical illustrator, for the excellent illustrations, anatomic drawings and thematic designs. I appreciate the many people at

Lippincott Williams & Wilkins who have helped me, especially Charley Mitchell, with whom I have worked for nearly two decades, and consider the best editor in medical book publishing. I extend my gratitude to Anne Sydor, Nicole Dernoski, Sonya Seigafuse, Nicole Walz, and Tracey Becker for their dedication and commitment during the editorial process to enthusiastically and skillfully produce the manuscript. I acknowledge the outstanding work of Barbara Stabb who so diligently and expertly worked closely with me to do the final page layout and formatting of this book that makes its first appearance in full color. I acknowledge the efforts of my mentors and colleagues—Dean Sherman Mellinkoff, Drs. J. Donald Woodruff, Kenneth J. Ryan, Isaac Schiff, J. George Moore, William J. Dignam, Gautam Chaudhuri, and Neville F. Hacker. Each of these physicians and scholars provided me with guidance and encouragement. My special thanks to Nicole Kidman, the chair of the advisory board for the UCLA Women's Reproductive Cancer Program—whose support and friendship helped stimulate this project.

The publication of this book coincides with a major change in my medical career, which took me along the east coast from Brown to Johns Hopkins and then to Harvard, before providing a lengthy and rewarding sojourn at UCLA. After more than 26 years at UCLA, I moved to Stanford University School of Medicine to become the Professor and Chair of the Department of Obstetrics and Gynecology. I welcome the opportunity there to participate in teaching the specialty of gynecology, researching the related sciences, and delivering patient care while learning from my new colleagues.

I look forward to the continued positive impact of the specialty on women's health throughout the world. It is my fervent hope that this work will benefit all women and reduce the numbers of those who are afflicted with diseases of the female reproductive tract. To that end, this book is offered as a resource to assist and encourage all who study the specialty of gynecology.

Jonathan S. Berek

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1

Initial Assessment and Communication

Jonathan S. Berek

Paula J. Adams Hillard



- **We are all products of our environment, our background, and our culture. The importance of ascertaining the patient's general, social, and familial situation cannot be overemphasized. The physician should avoid being judgmental, particularly with respect to questions about sexual practices and sexual orientation.**
- **Good communication is essential to patient assessment and treatment. The foundation of communication is based on key skills: empathy, attentive listening, expert knowledge, and rapport. These skills can be learned and refined.**
- **The Hippocratic Oath demands that physicians be circumspect with all patient-related information. For physician–patient communication to be effective, the patient must feel that she is able to discuss her problems fully.**
- **Different styles of communication may affect the physician's ability to perceive the patient's status and to achieve the goal of optimal assessment and**

successful treatment. The intimate and highly personal nature of many gynecologic conditions requires particular sensitivity to evoke an honest response.

- **Some patients lack accurate information about their illness. Lack of full understanding of an illness can produce dissatisfaction with medical care, increased anxiety, distress, coping difficulties, unsuccessful treatment, and poor treatment response.**
- **After a dialogue has been established, the patient assessment proceeds with obtaining a complete history and performing a physical examination. Both of these aspects of the assessment rely on good patient–physician interchange and attention to details.**
- **At the completion of the physical examination, the patient should be informed of the findings. When the results of the examination are normal, the patient can be reassured accordingly. When there is a possible abnormality, the patient should be informed immediately; this discussion should take place after the examination with the patient clothed.**

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The practice of gynecology requires many skills. In addition to medical knowledge, the gynecologist should develop interpersonal and communication skills that promote patient–physician interaction and trust. The assessment must be of the “whole patient,” not only of her general medical status. It should include any apparent medical condition as well as the psychological, social, and family aspects of her situation. **To view the patient in the appropriate context, environmental and cultural issues that affect the patient must be taken into account.** This approach is of value in routine assessments, providing opportunities for preventive care and counseling on an ongoing basis, as well as in the assessment of medical conditions.

Variables that Affect Patient Status

Many external variables exert an influence on the patient and on the care she receives. Some of these factors include the patient's “significant others”—her family, friends, and personal and intimate relationships (Table 1.1). **These external variables also include psychological, genetic, biologic, social, and economic issues.** Factors that affect a patient's perception of disease and pain and the means by which she has been taught to cope with illness include her education, attitudes, understanding of human reproduction and sexuality, family history of disease, and, in some cases, need for attention (1,2,3). Cultural factors, socioeconomic status, religion, ethnicity, and sexual orientation are important considerations in understanding the patient's response to her care.

We are all products of our environment, our background, and our culture. The importance of ascertaining the patient's general, social, and familial situation cannot be overemphasized (4). The context of the family can and should be ascertained directly. The family history should include a careful analysis of those who have had significant illnesses, such as cancer. The patient's understanding of key events in the family medical history and how she relates to them are also important. The psychological and sexual practices of the patient should be understood, and her functional level of satisfaction in these areas should be determined. **The physician should avoid being judgmental, particularly with respect**

to questions about sexual practices and sexual orientation (see Chapters 11 and 12).

Table 1.1 Variables that Influence the Status of the Patient	
Patient	
Age	
History of illness	
Attitudes and perceptions	
Sexual orientation	
Habits (e.g., use of alcohol, tobacco, and other drugs)	
Family	
Patient's status (e.g., married, separated, living with a partner, divorced)	
Caregiving (e.g., young children, children with disabilities, aging parents)	
Siblings (e.g., number, ages, closeness of relationship)	
History (e.g., disease)	
Environment	
Social environment (e.g., community, social connectedness)	
Economic status (e.g., poverty, insuredness)	
Religion (e.g., religiosity, spirituality)	
Culture and ethnic background (e.g., first language, community)	
Career (e.g., work environment, satisfaction, responsibilities, stress)	

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Communication

Good communication is essential to patient assessment and treatment. The patient–physician relationship is based on communication conducted in an open, honest, and careful manner that allows the patient's situation and problems to be accurately understood and effective solutions developed collaboratively. Good communication requires patience, dedication, and practice, and involves both listening and communicating verbally and nonverbally.

The foundation of communication is based on key skills: empathy, attentive listening, expert knowledge, and rapport. These skills can be learned and refined (4,56). Once the initial relationship with the patient is established, the physician must vigilantly pursue interviewing techniques that create opportunities to foster an understanding of the patient's concerns (7). Trust is the fundamental element that encourages the patient to communicate her feelings, concerns, and thoughts openly, without withholding information (8).

Although there are many styles of interacting with patients, and each physician must develop and determine the best way that he or she can relate to patients, physicians must convey that they are able and willing to listen and that they receive the information with utmost confidentiality (1). **The Hippocratic Oath demands that physicians be circumspect with all patient-related information.** The Health Insurance Portability and Accountability Act (HIPAA), which took effect in 2003, established national standards that were intended to protect the privacy of personal health information. Most physicians agree that there must be room for professional judgment to prevent such laws from becoming a bureaucratic impediment to patient care (9).

Communication Skills

It is essential for the physician to communicate with a patient in a manner that allows her to continue to seek appropriate medical attention. Not only the words used, but also the patterns of speech, the manner in which the words are delivered, even body language and eye contact are important aspects of the patient–physician interaction. The traditional role of the physician has been paternalistic, with the physician being expected to deliver direct commands or “orders” and specific guidance on all matters (4). Patients are now appropriately demanding more balanced communication with their physicians, and although they do not in most cases command an understanding of medicine, they do expect to be treated with appropriate deference, respect for their intellect, and a manner more equal in stature with the physician (10). As a result of electronic access to medical information, patients sometimes have more specific medical knowledge of a given medical problem than the physician does. When this is the case, the physician must avoid feeling defensive. The patient often lacks a broader knowledge of the context of the problem, awareness of the variable reliability of different electronic sources of information, an ability to assess a given study or journal report in an historical context or in comparison with other studies on the topic, knowledge of the interactions of drugs, an ability to have an intellectual distance from the topic that allows objectivity, and experience in the practice of the art and science of medicine. The physician possesses these skills and knowledge, whereas the patient has an intense personal interest in her specific medical condition. **A collaborative relationship that allows patients greater involvement in the relationship potentially can lead to better health outcomes** (1,11,12).

Table 1.2 Important Components of Communication between the Patient and Physician: The Physician's Role	
<i>The Physician Is:</i>	<i>The Physician Is Not:</i>
A good listener	Confrontational
Empathetic	Combative
Compassionate	Argumentative
Honest	Condescending
Genuine	Overbearing
Respectful	Dogmatic
Fair	Judgmental
Facilitative	Paternalistic
<i>The Physician Uses:</i>	
Understandable language	
Appropriate body language	
A collaborative approach	
Open dialogue	
Appropriate emotional content	
Humor and warmth	

Physician–Patient Interaction

The pattern of the physician's speech can influence interactions with the patient.

Some important components of effective communication between patients and physicians are presented in Table 1.2. There is evidence that not only can scientifically derived and empirically validated interview skills be taught and learned, but also that these skills can result

in improved outcomes (6). A list of such skills is found in Table 1.3.

For physician–patient communication to be effective, the patient must feel that she is able to discuss her problems fully. Time constraints imposed by the pressures of office scheduling to meet economic realities make this difficult; both the physician and the patient frequently need to reevaluate their priorities. If the patient perceives that she participates in decision making and that she is given as much information as possible, she will respond to the mutually derived treatment plan with lower levels of anxiety and depression, embracing it as a collaborative plan of action. She should be able to propose alternatives or modifications to the physician's recommendations that reflect her own beliefs and attitudes. There is ample evidence that patient communication, understanding, and treatment outcomes are improved when discussions with physicians are more dialogue than lecture. In addition, when patients feel they have some room for negotiation, they tend to retain more information regarding health-care recommendations (13). The concept of collaborative planning between patients and physicians has been embraced as a more effective alliance than the previous model in which physicians issued orders (13). The patient thus becomes more vested, determining health-care choices. For example, decisions about the risks and benefits of menopausal hormone therapy must be discussed in the context of an individual's health and family history as well as her personal beliefs and goals. Whether the benefits outweigh the potential risks ultimately is determined by the woman, who decides whether to use such therapy. Whereas most women prefer shared decision making in the face of uncertainty, with an evidence-based discussion of her risks and benefits, others want a more directive approach (14). **The physician's challenge is to be able to personalize the interaction and communication.**

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<i>Preparing the Environment</i>	<i>Negotiating a Priority Problem</i>
Create privacy	Ask patient for priorities
Eliminate noise and distractions	State own priorities
Provide comfortable seating at equal eye level	Establish mutual interests
Provide access	Reach agreement on order of addressing issues
<i>Preparing Oneself</i>	<i>Developing a Narrative Thread</i>
Eliminate distractions and interruptions	Develop personal ways of asking patient to tell her story
Focus	Ask when last felt healthy
Self-hypnosis	Ask about entire course of illness
Meditation	Ask about recent episode or typical episode
Constructive imaging	<i>Establishing the Life Context of the Patient</i>
Let intrusive thoughts pass through	Use first opportunity to inquire about personal and social details
<i>Observation</i>	Flesh out developmental history
Create a personal list of categories of observation	Learn about patient's support system
Practice in a variety of settings	Learn about home, work, neighborhood, safety
Notice physical signs	<i>Establishing a Safety Net</i>
Presentation	Memorize complete review of systems

Affect	Review issues as appropriate to specific problem
What is said and not said	Presenting Findings and Options
Greeting	Be succinct
Create a personal stereotypical beginning	Ascertain patient's level of understanding, cognitive style
Introduce oneself	Ask patient to review and state understanding
Check the patient's name and how it is said	Summarize and check
Create a positive social setting	Tape record and give tape to patient
Introduction	Ask patient's perspectives
Explain one's role and purpose	Negotiating Plans
Check patient's expectation	Activate patient
Negotiate about differences in perspective	Agree on what is feasible
Be sure expectations are congruent with patient's	Respect patient's choices whenever possible
Detecting and Overcoming Barriers to Communication	Closing
Develop personal list of barriers to look for	Ask patient to review plans and arrangements
Include appropriate language	Clarify what to do in the interim
Physical impediments such as deafness, delirium	Schedule next encounter
Include cultural barriers	Say goodbye
Recognize patient's psychological barriers, such as shame, fear, and paranoia	
Surveying Problems	
Develop personal methods of initiation of problem listing	
"Ask What else?" until problems are elicited	
<p>^a Lipkin M Jr. Physician-patient interaction in reproductive counseling. <i>Obstet Gynecol</i> 1996;88:31S-40S.</p> <p>Derived from Lipkin M, Frankel RM, Beckman HB, et al. Performing the interview. In: Lipkin M, Putnam SM, Lazare A, eds. <i>The medical interview: clinical care, education, and research</i>. New York, NY: Springer-Verlag, 1995:65-82.</p>	

There is evidence that when patients are heard and understood, when they become more vocal and inquisitive, their health improves (7). Participation facilitates investment and empowerment. **Good communication is essential to the maintenance of a relationship between the patient and physician that fosters ongoing care.**

Health maintenance, therefore, can be linked directly to the influence of positive interactions between the physician and patient. Women who are comfortable with their physician may be more likely to raise issues or concerns or convey information about potential health risks and may be more receptive to the physician's recommendations. This degree of rapport may promote the effectiveness of health interventions, including behavior modification. It also helps ensure that patients return for regular care because they feel the physician is genuinely interested in their welfare.

When patients are ill, they feel vulnerable, physically and psychologically exposed, and powerless. The physician, by virtue of his or her knowledge and status, has power that can be intimidating. It is essential that the physician be aware of this disparity so the "balance of

power" does not shift too far away from the patient. Shifting it back from the physician to the patient may help improve outcomes (1,11,12). Physicians' behaviors can suggest that they are not respectful of the patient. Such actions as failing to maintain scheduled appointment times, routinely holding substantive discussions with the patient undressed, or speaking to her from a standing position while she is lying down or in the lithotomy position can emphasize the imbalance of power in the relationship.

In assessing the effects of the patient–physician interaction on the outcome of chronic illness, three characteristics associated with better health care outcomes have been identified (12):

- **Empathetic physician and a high level of patient involvement in the interview**
- **Expression of emotion by both patient and physician**
- **Provision of information by the physician in response to the patient's inquiries**

Among patients with diabetes, these characteristics resulted in improved diastolic blood pressure and reduction of hemoglobin A_{1c}. The best responses were achieved when an empathetic physician provided as much information and clarification as possible, responded to the patients' questions openly and honestly, and expressed a full range of emotions, including humor. Responses improved when the relationship was not dominated by the physician (12).

In studies of gender and language, men tend to talk more than women, successfully interrupt women, and control the topics of the conversation (15). As a result, male physicians may tend to take control, and the imbalance of power may be magnified in the field of obstetrics and gynecology, in which all the patients are women. Male physicians may be more assertive than female physicians are. Men's speech tends to be characterized by interruptions, command, and lectures, and women's speech is characterized by silence, questions, and proposals (16,17). Some patients may simply feel more reticent in the presence of a male physician, whereas others may be more forthcoming with a male than a female physician (18). Women's preference for a male or female physician may be based on sex as well as experience, competency, communication styles, and other skills (19,20). Although these generalizations clearly do not apply to all physicians, they can raise awareness about the various styles of communication and how they shape the physician–patient relationship (21,22). These patterns indicate **the need for all physicians, regardless of their sex, to be attentive to their style of speech because it may affect their ability to elicit open and free responses from their patients** (21,23). Women tend to speak openly to express

their feelings and to have them validated and shared in an attempt to gain understanding of their concerns (13,15,16).

Different styles of communication may affect the physician's ability to perceive the patient's status and to achieve the goal of optimal assessment and successful treatment. The intimate and highly personal nature of many gynecologic conditions requires particular sensitivity to evoke an honest response.

Style

The art of communication and persuasion is based on mutual respect and development of the patient's understanding of the circumstances of her health (7). Insight is best achieved when the patient is encouraged to question her physician and when she is not pressured to make decisions (1,13). Patients who feel "backed into a corner" have the lowest compliance with recommended treatments (11).

Following are techniques to help achieve rapport with patients:

- **Use positive language (e.g., agreement, approval, and humor).**
- **Build a partnership (e.g., acknowledgment of understanding, asking for opinions, paraphrasing, and interpreting the patient's words).**
- **Ask rephrased questions.**
- **Give complete responses to the patient's questions.**

The manner in which a physician guides a discussion with a patient will determine the patient's level of understanding and her ability to successfully complete therapy.

The term *compliance* has long been used in medicine; it suggests that the patient will follow the physician's recommendations or "orders." The term has been criticized as being overly paternalistic; an alternative term, *adherence* to therapy, has been proposed (24,25). This term still carries the connotation that the therapy will be dictated by the physician. A more collaborative approach is suggested by the phrase *successful use* of therapy, which can be credited mutually to the physician and the patient. With this phrase, however, the ultimate success of the therapy appropriately accrues to the patient (26). If a directive is given to take a prescribed medication without a discussion of the rationale for its use, patients may not comply, particularly if the instructions are confusing or difficult to follow (13). Difficulties in compliance may be dictated by practical considerations: Nearly everyone finds a qid regimen more difficult than daily use. A major factor in successful compliance is simplicity of the regimen (27). Practical factors that affect successful use include financial considerations, insurance coverage, and even literacy (28). A discussion and understanding of the rationale for therapy along with the potential benefits and risks are necessary components of successful use; however, it may not be sufficient in the face of practical barriers. The specifics of when and how to take medication, including what to do when medication is missed, also have an impact on successful use.

The style of the presentation of information is key to its effectiveness. As noted, the physician should establish a balance of power in the relationship, including conducting serious discussions about diagnosis and management strategies when the patient is fully clothed and face-to-face with the physician in a private room. Body language is also important in interactions with patients. The physician should avoid an overly casual manner, which can communicate a lack of caring or compassion. The patient should be viewed directly and spoken to with eye contact so that the physician is not perceived as "looking off into the distance" (7).

Laughter and Humor

Humor is an essential component that promotes open communication. It can be either appropriate or inappropriate. Appropriate humor allows the patient to diffuse anxiety and understand that (even in difficult situations) laughter can be healthy (29). Inappropriate humor would horrify, disgust, or offend a patient or generally make her uncomfortable or seem disrespectful. Laughter can be used as an appropriate means of relaxing the patient and making her feel better.

Laughter is a "*metaphor for the full range of the positive emotions*" (29). It is the response of human beings to incongruities and one of the highest manifestations of the cerebral process. It helps to facilitate the full range of positive emotions—love, hope, faith, the will to live, festivity, purpose, and determination (29). Laughter is a physiologic response, a release that helps us all feel better and allows us to accommodate the collision of logic and absurdity. Illness, or the prospect of illness, heightens our awareness of the incongruity between our existence and our ability to control the events that shape our lives and our outcomes. We use laughter to combat stress, and stress reduction is an essential mechanism used to cope with illness.

Strategies for Improving Communication

All physicians should appreciate the importance of the art of communication during the medical interview. It is essential that interactions with patients are professional, honorable, and honest. Issues that have been reported to be important to *physicians* regarding patient–physician interactions are presented in Table 1.4. Similarly, patients have suggested the importance of many of these same issues in facilitating participatory decision making (30).

Rank	Physicians' Support Services	Always or Often (%)	Rarely or Never (%)
1	Answering the patient's questions about the disease and its treatment, side effects, and possible outcomes	99	1
2	Making sure that the patient clearly understands the explanation of the medical treatment procedures	99	1
3	Encouraging the patient to develop an attitude of hope and optimism concerning treatment outcome	95	5
4	Adjusting treatment plans to enhance compliance when the patient exhibits noncompliance	88	12
5	Directly counseling family members	87	13
6	Continuing to serve as primary physician when the patient receives supplementary treatment at another facility	85	15
7	Providing referral to social support groups	83	17
8	Providing the patient with educational materials	81	19
9	Helping the patient develop methods to improve the quality of his or her life	74	26

10	Assisting the patient in determining which of his or her coping mechanisms are most productive and helping to activate them	62	38
11	Providing referral to psychological counseling services	57	43

^aResults of a physician survey of 649 oncologists in regard to patient-physician communication.

Modified from Cousins N. Head first: the biology of hope and the healing power of the human spirit. New York, NY: Penguin Books, 1989:220, with permission.

P.11

Following are some general guidelines that can help to improve communication:

- **Listen more and talk less.**
- **Encourage the pursuit of topics introduced by and important to patients.**
- **Minimize controlling speech habits such as interrupting, issuing commands, and lecturing.**
- **Seek out questions and provide full and understandable answers.**
- **Become aware of any discomfort that arises in an interview, recognize when it originates in an attempt by the physician to take control, and redirect that attempt.**
- **Assure patients that they have the opportunity to discuss their problem fully.**
- **Recognize when patients may be seeking empathy and validation of their feelings rather than a solution. Sometimes all that is necessary is to be there as a compassionate human being.**

In conducting interviews, it is important for the physician to understand the patient's concerns. Given the realities of today's busy office schedules, an additional visit may be required to discuss some issues fully. In studies of interviewing techniques it has been shown that although clinicians employ many divergent styles, the successful ones tend to look for "windows of opportunity" (i.e., careful, attentive listening with replies or questions at opportune times) (7). This skill of communication is particularly effective in exploring psychological and social issues during brief interviews. The chief skill essential to allowing the physician to perceive problems is the ability to listen attentively.

An interview that permits maximum transmission of information to the physician is best achieved by the following approach (7):

- **Begin the interview with an open-ended question.**
-

As the patient begins to speak, pay attention not only to her answers but also to her emotions and general body language.

- **Extend a second question or comment, encouraging the patient to talk.**

- **Allow the patient to respond without interrupting, perhaps by employing silence, nods, or small facilitative comments, encouraging the patient to talk while the physician is listening.**

- **Summarize and express empathy and understanding at the completion of the interview.**

Attentiveness, rapport, and collaboration characterize good medical interviewing techniques. Open-ended questions ("How are you doing?" "How are things at home?" "How does that make you feel?") generally are desirable, particularly when they are coupled with good listening skills (31).

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Premature closure of an interview and inability to get complete information to the patient may occur for several reasons (7). It may arise from a lack of recognition of the patient's particular concern, from not providing appropriate opportunity for discussion, from the physician becoming uncomfortable in sharing the patient's emotion, or perhaps from the physician's lack of confidence that he or she can deal with the patient's concern. One of the principal factors undermining the success of the interview is lack of time. This is a realistic concern as perceived by physicians, but skilled physicians can facilitate considerable interaction even in a short time by encouraging open communication (32).

Some patients lack accurate information about their illness. Lack of full understanding of an illness can produce dissatisfaction with medical care, increased anxiety, distress, coping difficulties, unsuccessful treatment, and poor treatment response (33,34,35). As patients increasingly request more information about their illnesses and more involvement in decisions about their treatment, and as physicians attempt to provide more open negotiation, communication problems become more significant. Although patients vary in their intellectual capacity, medical sophistication, levels of denial and anxiety, and their own communication skills, poor patient understanding stems as well from poor physician communication techniques, lack of consultation time, and in some cases, the withholding of information considered detrimental to patient welfare (33).

If clinical findings or confirmatory testing strongly suggest a serious condition (e. g., malignancy), the gravity and urgency of this situation must be conveyed in a manner that does not unduly alarm or frighten the individual. Honest answers should be provided to any specific questions the patient may want to discuss (34,35).

Allowing time for questions is important, and scheduling a follow-up visit to discuss treatment options after the patient has had an opportunity to consider the options and recommendations often is valuable (34,35). The patient should be encouraged to bring a partner or family member with her to provide moral support, to serve as another listener to hear and understand the discussion, and to assist with questions. The patient should also be encouraged to write down any questions or concerns she may have and bring them with her to a subsequent visit; important issues may not come to mind easily during an office visit. If the patient desires a second opinion or if a second opinion is mandated by her insurance carrier, it should always be facilitated. Physicians should not feel threatened by patient attempts to gain information and knowledge.

Valuable information can be provided by interviews with ancillary support staff and by providing pamphlets and other materials produced for patient education. Some studies have demonstrated that the use of pamphlets is highly effective in promoting an understanding of the condition and treatment options. Others have shown that the use of audiotapes and videotapes has a positive impact on knowledge and can decrease anxiety (33).

There are numerous medicine Web sites that can be accessed electronically, although the accuracy of the information is variable and must be carefully reviewed by physicians before recommending to patients. Physicians should be familiar with Internet sources of accurate information and be prepared to provide the addresses of these sites if the patient expresses interest (36).

The relationship between the patient and her physician, as with all aspects of social interchange, is subject to constant change. The state of our health is dynamic. Many of us are fortunate to be in a good state of health for much of our lives, but some are not so fortunate. **Open communication between patient and physician can help achieve maximum effectiveness in diagnosis, treatment, and compliance for all patients.**

P.13

Talk to the heart, speak to the soul.
Look to the being and embrace the figure's form.
Reach deeply, with hands outstretched.
Talk intently, to the seat of wisdom,
as life resembles grace.

Achieve peace within a fragile countenance.
Seek the comfort of the placid hour
Through joyous and free reflection
know the other side of the flesh's frame.

JSB

History and Physical Examination

After a dialogue has been established, the patient assessment proceeds with obtaining a complete history and performing a physical examination. Both of these aspects of the assessment rely on good patient–physician interchange and attention to details. During the history and physical examination, risk factors that may require special attention should be identified. These factors should be reviewed with the patient in developing a plan for her future care (see Chapter 8).

Depending on the setting—ambulatory care/office, inpatient hospitalization, or outpatient surgical center—record keeping is typically facilitated by written forms, which provide prompts for important elements of the medical, family, and social history. Increasingly electronic medical records are being developed. However, one challenge is that paper and electronic records do not always “mesh,” and both paper and electronic records are periodically unavailable. Efforts to develop patient-held medical records have not yet been widely adopted. Self-completed forms may encourage a collaborative approach to preventive care (37).

History

After the chief complaint and characteristics of the present illness have been ascertained, the medical history of the patient should be obtained. It should include her complete medical and surgical history, her reproductive history (including menstrual and obstetric history), and a thorough family and social history.

A technique for obtaining information about the present illness is presented in Table 1.5.

The physician should consider what other members of the health-care team might be helpful in completing the evaluation and providing care. Individuals who interact with the patient in the office—from the receptionists to medical assistants, nurses, advance practice nurses (nurse practitioners or nurse-midwives)—can all contribute to the patient's care and may provide additional information or insight or be appropriate clinicians for providing follow-up. The role that each of these individuals plays in a given office or health-care setting may not be apparent to the patient; care should be taken with introductions, and it may be necessary to discuss the roles and functions of each individual. In some cases, referral to a nutritionist, physical or occupational therapist, social worker, psychologist, psychiatrist, or sex counselor would be helpful. Referral to or consultations with these clinicians as well as with physicians in other specialty areas should be addressed as needed. The nature of the relationship between the obstetrician/gynecologist and the patient should be clarified. Some women have a primary clinician whom they rely on for primary care. Other women, particularly healthy women of reproductive age, consider their obstetrician-gynecologist their primary clinician. The individual physician's comfort with this role should be discussed and clarified at the initial visit and revisited periodically as required in the course of care. These issues are covered in Section III, Preventative and Primary Care (see Chapters 8,9,10,11,12 through, 13). Laboratory testing for routine care and high-risk factors are presented in Chapter 8.

Table 1.5 Technique of Taking the History of the Present Illness

- 1. The technique used in taking the history of the present illness varies with the patient, the patient's problem, and the physician. Allow the patient to talk about her chief symptom.** Although this symptom may or may not represent the real problem (depending on subsequent evaluation), it is usually uppermost in the patient's mind and most often constitutes the basis for the visit to the physician.

During the phase of the interview, establish the temporal relation of the chief symptom to the total duration of the illness. Questions such as, "*Then up to the time of this symptom, you felt perfectly well?*" may elicit other symptoms that may antedate the chief one by days, months, or years. In this manner, the patient may recall the date of the first appearance of illness.

Encourage the patient to talk freely and spontaneously about her illness from the established date of onset. Do not interrupt the patient's account, except for minor promptings such as, "*When did it begin?*" and "*How did it begin?*," which will help in developing chronologic order in the patient's story.

After the patient has furnished her spontaneous account (and before the next phase of the interview), it is useful to employ questions such as, "*What other problems have you noticed since you became ill?*" The response to this question may reveal other symptoms not yet brought forth in the interview.

Thus, in the first phase of the interview, the physician obtains an account of the symptoms as the patient experiences them, without any bias being introduced by the examiner's direct questions. Information about the importance of the symptoms to the patient and the patient's emotional reaction to her symptoms are also revealed.

2. **Because all available data regarding the symptoms are usually not elicited by the aforementioned techniques, the initial phase of the interview should be followed by a series of direct and detailed questions concerning the symptoms described by the patient.** Place each symptom in its proper chronologic order and then evaluate each in accordance with the directions for analyzing a symptom.

In asking direct questions about the details of a symptom, take care not to suggest the nature of the answer. This particularly refers to questions that may be answered "yes" or "no." If a leading question should be submitted to the patient, the answer must be assessed with great care. Subject the patient to repeated cross-examination until you are completely satisfied that the answer is not given just to oblige you.

Finally, before dismissing the symptom under study, inquire about other symptoms that might reasonably be expected under the clinical circumstances of the case. Symptoms specifically sought but denied are known as negative symptoms. These negative symptoms may confirm or rule out diagnostic possibilities suggested by the positive symptoms.

3. **The data secured by the techniques described in the first two phases of the interview should now suggest several diagnostic possibilities.** Test these possibilities further by inquiring about other symptoms or events that may form part of the natural history of the suspected disease or group of diseases.
4. **These techniques may still fail to reveal all symptoms of importance to the present illness, especially if they are remote in time and seemingly unrelated to the present problem.** The review of systems may then be of considerable help in bringing forth these data. A positive response from the patient on any item in any of the systems should lead immediately to further detailed questioning.
5. **Throughout that part of the interview concerning the present illness, consider the following factors:**
 - a. **The probable cause of each symptom or illness, such as emotional stress, infection, neoplasm.** Do not disregard the patient's statements of causative factors. Consider each statement carefully, and use it as a basis for further investigation. When the symptoms point to a specific infection, direct inquiry to water, milk, and foods eaten; exposure to communicable diseases, animals, or pets; sources of sexually transmitted disease; or residence or travel in the tropics or other regions where infections are known to exist. In each of the above instances, ascertain, if possible, the date of exposure, incubation period, and symptoms of invasion (prodromal symptoms).
 - b. **The severity of the patient's illness, as judged either by the presence of systemic symptoms, such as weakness, fatigue, loss of weight, or by a change in personal habits.** The latter includes changes in sleep, eating, fluid intake, bowel movements, social activities, exercise, or work. Note the dates the patient discontinued her work or took to bed. Is she continuously confined to bed?
 - c. **Determine the patient's psychological reaction to her illness (anxiety, depression, irritability, fear) by observing how she relates her story as well as her nonverbal behavior.** The response to a question such as, "*Have you any particular theories about or fear of what may be the matter with you?*" may yield important clues relative to the patient's understanding and feeling about her illness. The reply may help in the management of the patient's problem and allow the physician to give advice according to the patient's understanding of her ailment.

Hochstein E, Rubin AL. *Physical diagnosis*. New York, NY: McGraw-Hill, 1964:9–11, with permission.

Physical Examination

A thorough general physical examination typically is performed at the time of the initial visit, on a yearly basis, and as needed throughout the course of treatment (Table 1.6.). The extent of the physical examination is often dictated by the patient's primary concerns and symptoms. For example, for healthy teens without symptoms who are requesting oral contraceptives before the initiation of intercourse, a gynecologic exam is not necessarily required. Some aspects of the examination—such as assessment of vital signs in addition to measurement of height, weight, and blood pressure and calculation of a body mass index—are performed routinely during most office visits. Typically, examination of the breast, abdomen, and a complete examination of the pelvis are considered to be the essential parts of the gynecologic examination.

Abdominal Examination

With the patient in the supine position, an attempt should be made to have her relax as much as possible. Her head should be leaned back and supported gently by a pillow so that she does not tense her abdominal muscles.

The abdomen should be inspected for signs of an intra-abdominal mass, organomegaly, or distention that would, for example, suggest ascites or intestinal obstruction. Auscultation of bowel sounds, if deemed necessary to ascertain the nature of the bowel sounds, should precede palpation. The frequency of intestinal sounds and their quality should be noted. In a patient with intestinal obstruction, "rushes," as well as the occasional high-pitched sound, can be heard. Bowel sounds associated with an ileus may occur less frequently but at the same pitch as normal bowel sounds.

The abdomen is palpated to evaluate the size and configuration of the liver, spleen, and other abdominal contents. Evidence of fullness or mass effect should be noted. This is particularly important in evaluating patients who may have a pelvic mass and in determining the extent of omental involvement, for example, with metastatic ovarian cancer. A fullness in the upper abdomen could be consistent with an "omental cake." All four quadrants should be carefully palpated for any evidence of mass, firmness, irregularity, or distention. A systematic approach should be used (e.g., clockwise, starting in the right upper quadrant). Percussion should be used to measure the dimensions of the liver. The patient should be asked to inhale and exhale during palpation of the edge of the liver.

Pelvic Examination

The pelvic examination usually is performed with the patient in the dorsal lithotomy position (Fig. 1.1). The patient's feet should rest comfortably in stirrups with the edge of the buttocks at the lower end of the table so that the vulva can be readily inspected and the speculum can be inserted in the vagina without obstruction from the table. Raising the head of the examination table, if possible, may facilitate relaxation. Drapes should be placed to provide a measure of cover for the patient's legs but should be depressed over the abdomen to allow observation of the patient's expression and to facilitate communication.

Before each step of the examination, the patient should be informed of what she will feel next:

"First you'll feel me touch your inner thighs; next I'll touch the area around the outside of your vagina." The vulva and perineal area should then be carefully inspected. Evidence of any lesions, erythema, pigmentation, masses, or irregularity should be noted. The skin quality should be noted as well as any signs of trauma, such as excoriations or ecchymosis.

The presence of any visible lesions should be quantitated and carefully described with regard to their full appearance and characteristics on palpation (i.e., mobility, tenderness, consistency).

A drawing of the location of skin lesions is helpful. Ulcerative or purulent lesions of the vulva should be evaluated and cultured as outlined in subsequent chapters, and biopsy should be performed on any lesions.

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Table 1.6 Method of the Female Pelvic Examination

The patient is instructed to empty her bladder. She is placed in the lithotomy position (Fig. 1.1) and draped properly. The examiner's right or left hand is gloved, depending on his or her preference. The pelvic area is illuminated well, and the examiner faces the patient. The following order of procedure is suggested for the pelvic examination:

A. External genitalia

1. Inspect the mons pubis, labia majora, labia minora, perineal body, and anal region for characteristics of the skin, distribution of the hair, contour, and swelling. Palpate any abnormality.
2. Separate the labia majora with the index and middle fingers of the gloved hand and inspect the epidermal and mucosal characteristics and anatomic configuration of the following structures in the order indicated below:
 - a. Labia minora
 - b. Clitoris
 - c. Urethral orifice
 - d. Vaginal outlet (introitus)
 - e. Hymen
 - f. Perineal body
 - g. Anus
3. If disease of the Skene glands is suspected, palpate the gland for abnormal excretions by milking the undersurface of the urethra through the anterior vaginal wall. Examine the expressed excretions by microscopy and cultures.

If there is a history of labial swelling, palpate for a diseased Bartholin gland with the thumb on the posterior part of the labia majora and the index finger in the vaginal orifice. In addition, sebaceous cysts, if present, can be felt in the labia minora.

B. Introitus

With the labia still separated by the middle and index fingers, instruct the patient to bear down. Note the presence of the anterior wall of the vagina when a cystocele is present or bulging of the posterior wall when a rectocele or enterocele is present. Bulging of both may accompany a complete prolapse of the uterus.

The supporting structure of the pelvic outlet is evaluated further when the bimanual

pelvic examination is done.

C. **Vagina and cervix**

Inspection of the vagina and cervix using a speculum should always precede palpation.

The instrument should be warmed with tap water—not lubricated—if vaginal or cervical smears are to be obtained for the test or if cultures are to be performed.

Select the proper size of speculum (Fig. 1.2), warmed and lubricated (unless contraindicated). Introduce the instrument into the vaginal orifice with the blades oblique, closed, and pressed against the perineum. Carry the speculum along the posterior vaginal wall, and after it is fully inserted, rotate the blades into a horizontal position and open them. Maneuver the speculum until the cervix is exposed between the blades. Gently rotate the speculum around its long axis until all surfaces of the vagina and cervix are visualized.

1. Inspect the vagina for the following:

- a. The presence of blood
- b. Discharge. This should be studied to detect trichomoniasis, monilia, and clue cells and to obtain cultures, primarily for gonococci and chlamydia.
- c. Mucosal characteristics (i.e., color, lesions, superficial vascularity, and edema)

The lesion may be:

1. Inflammatory—redness, swelling, exudates, ulcers, vesicles
 2. Neoplastic
 3. Vascular
 4. Pigmented—bluish discoloration of pregnancy (Chadwick's sign)
 5. Miscellaneous (e.g., endometriosis, traumatic lesions, and cysts)
 - d. Structural abnormalities (congenital and acquired)
- #### 2. Inspect the cervix for the same factors listed above for the vagina. Note the following comments relative to the inspection of the cervix:
- a. Unusual bleeding from the cervical canal, except during menstruation, merits an evaluation for cervical or uterine neoplasia.
 - b. Inflammatory lesions are characterized by a mucopurulent discharge from the os and redness, swelling, and superficial ulcerations of the surface.
 - c. Polyps may arise either from the surface of the cervix projecting into the vagina or from the cervical canal. Polyps may be inflammatory or neoplastic.
 - d. Carcinoma of the cervix may not dramatically change the appearance of the cervix or may appear as lesions similar in appearance to an inflammation. Therefore, a biopsy should be performed if there is suspicion of neoplasia.

D. **Bimanual palpation**

The pelvic organs can be outlined by bimanual palpation; the examiner places one hand on the lower abdominal wall and the finger(s) (one or two) (see Fig. 1.3) of the other hand in the vagina (or vagina and rectum in the rectovaginal examination) (see Fig. 1.4). Either the right or left hand may be used for vaginal palpation. The number of fingers inserted into the vagina should be based on what can comfortably be accommodated, the size and pliability of the vagina, and the weight of the patient. For example, adolescent, slender, and older patients might be best examined with a single finger technique.

1. Introduce the well-lubricated index finger and, in some patients, both the index and the middle

finger into the vagina at its posterior aspect near the perineum. Test the strength of the perineum by pressing downward on the perineum and asking the patient to bear down. This procedure may disclose a previously concealed cystocele or rectocele and descensus of the uterus.

Advance the fingers along the posterior wall until the cervix is encountered. Note any abnormalities of structure or tenderness in the vagina or cervix.

2. Press the abdominal hand, which is resting on the infraumbilical area, very gently downward, sweeping the pelvic structures toward the palpating vaginal fingers.

Coordinate the activity of the two hands to evaluate the body of the uterus for:

- a. Position
- b. Architecture, size, shape, symmetry, tumor
- c. Consistency
- d. Tenderness
- e. Mobility

Tumors, if found, are evaluated for location, architecture, consistency, tenderness, mobility, and number.

3. Continue the bimanual palpation, and evaluate the cervix for position, architecture, consistency, and tenderness, especially on mobility of the cervix. Rebound tenderness should be noted at this time. The intravaginal fingers should then explore the anterior, posterior, and lateral fornices.
4. Place the "vaginal" finger(s) in the right lateral fornix and the "abdominal" hand on the right lower quadrant. Manipulate the abdominal hand gently downward toward the vaginal fingers to outline the adnexa.

A normal tube is not palpable. A normal ovary (about 4 × 3 × 2 cm in size, sensitive, firm, and freely movable) is often not palpable. If an adnexal mass is found, evaluate its location relative to the uterus and cervix, architecture, consistency, tenderness, and mobility.

5. Palpate the left adnexal region, repeating the technique described previously, but place the vaginal fingers in the left fornix and the abdominal hand on the left lower quadrant.
6. Follow the bimanual examination with a rectovaginal–abdominal examination.

Insert the index finger into the vagina and the middle finger into the rectum very gently. Place the other hand on the infraumbilical region. The use of this technique makes possible higher exploration of the pelvis because the cul-de-sac does not limit the depth of the examining finger.

7. In patients who have an intact hymen, examine the pelvic organs by the rectal-abdominal technique.

E. Rectal examination

1. Inspect the perianal and anal area, the pilonidal (sacrococcygeal) region, and the perineum for the following aspects:
 - a. Color of the region (note that the perianal skin is more pigmented than the surrounding skin of the buttocks and is frequently thrown into radiating folds)
 - b. Lesions
 1. The perianal and perineal regions are common sites for itching. Pruritus ani is usually indicated by thickening, excoriations, and eczema of the perianal region and adjacent areas.
 2. The anal opening often is the site of fissures, fistulae, and external hemorrhoids.
 3. The pilonidal area may present a dimple, a sinus, or an inflamed pilonidal cyst.
2. Instruct the patient to "strain down" and note whether this technique brings into view previously

concealed internal hemorrhoids, polyps, or a prolapsed rectal mucosa.

3. Palpate the pilonidal area, the ischioanal fossa, the perineum, and the perianal region before inserting the gloved finger into the anal canal.

Note the presence of any concealed induration or tenderness in any of these areas.

4. Palpate the anal canal and rectum with a well-lubricated, gloved index finger. Lay the pulp of the index finger against the anal orifice and instruct the subject to strain downward. Concomitant with the patient's downward straining (which tends to relax the external sphincter muscle), exert upward pressure until the sphincter is felt to yield. Then, with a slight rotary movement, insinuate the finger past the anal canal into the rectum. Examine the anal canal systematically before exploring the rectum.
5. Evaluate the anal canal

- a. Tonus of the external sphincter muscle and the anorectal ring at the anorectal junction
- b. Tenderness (usually caused by a tight sphincter, anal fissure, or painful hemorrhoids)
- c. Tumor or irregularities, especially at the pectinate line
- d. Superior aspect: Reach as far as you can. Mild straining by the patient may cause some lesions, which are out of reach of the finger, to descend sufficiently low to be detected by palpation.
- e. Test for occult blood: Examine the finger after it is withdrawn for evidence of gross blood, pus, or other alterations in color or consistency. Smear the stool to test for occult blood (guaiac).

6. Evaluate the rectum

- a. Anterior wall

1. Cervix: size, shape, symmetry, consistency, and tenderness, especially on manipulation
2. Uterine or adnexal masses
3. Rectouterine fossa for tenderness or implants

In patients with an intact hymen, the examination of the anterior wall of the rectum is the usual method of examining the pelvic organs.

- b. Right lateral wall, left lateral wall, posterior wall, superior aspect; test for occult blood

Modified from Hochstein E, Rubin AL. Physical diagnosis. New York, NY: McGraw-Hill, 1964:342-353, with permission.

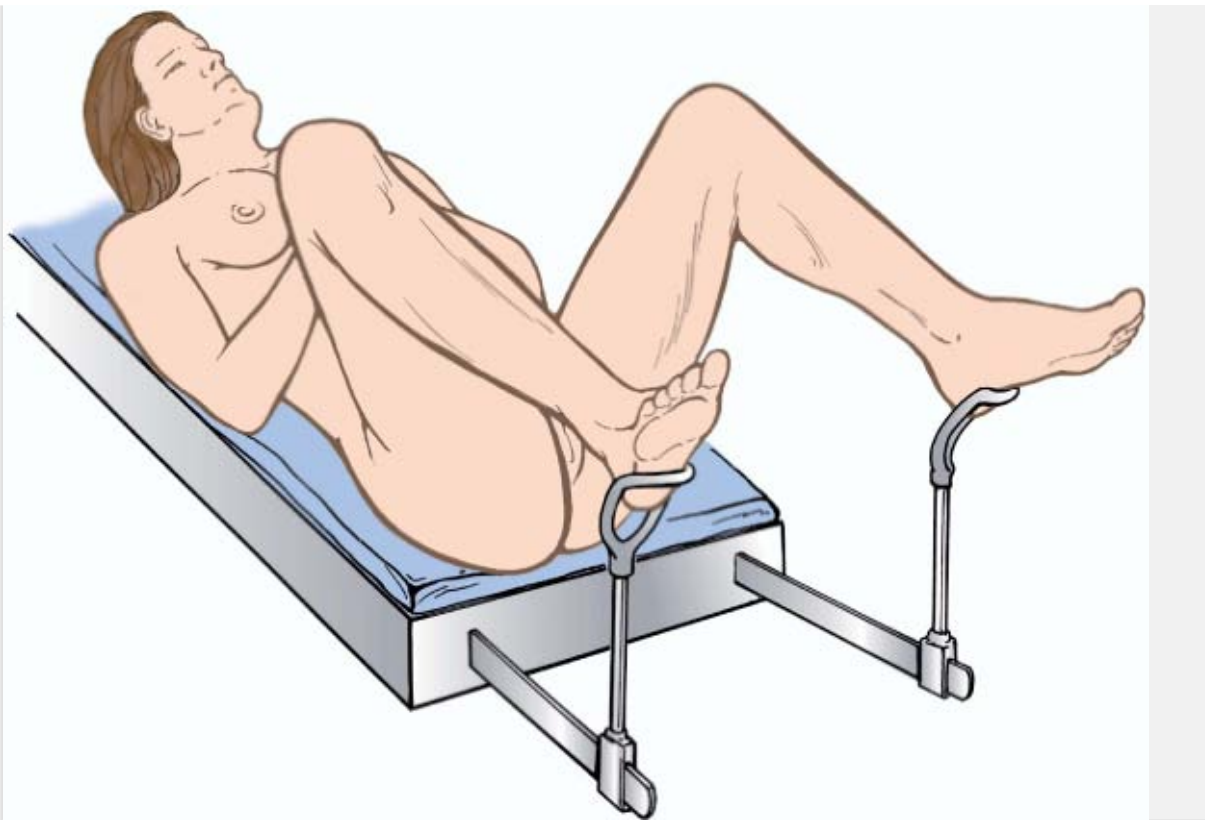


Figure 1.1 The lithotomy position for the pelvic examination.

After thorough visualization and palpation of the external genitalia, including the mons pubis and the perianal area, a speculum is inserted in the vagina. In a normal adult who is sexually active, a Pederson speculum is typically used. The types of specula that are used in gynecology are presented in Fig. 1.2. **In general, the smallest speculum necessary to produce adequate visualization should be used.** The larger Graves speculum may be required in women who have lax vaginal walls, are pregnant, or will be undergoing cervical or endometrial biopsies or procedures. In some women, a longer speculum (either Pederson or Graves) may facilitate visualization of the cervix in a manner that is less uncomfortable to the patient. If any speculum other than the typically sized specula is used, the patient should be informed so that she can remind the clinician before her next examination. The speculum should be warmed before it is inserted into the vagina; a heating pad or speculum warmer can be placed under the supply of specula. **If lubrication is required, warm water generally is sufficient.** The patient should be asked to relax the muscles of her distal vagina before the insertion of the speculum to facilitate the placement and to avoid startling her by this portion of the examination. After insertion, the cervix and all aspects of the vagina should be carefully inspected. Particular attention should also be paid to the vaginal fornices because lesions (e.g., warts) may be present in those areas and are not readily visualized.



Figure 1.2 Vaginal specula: 1, Graves extra long; 2, Graves regular; 3, Pederson extra long; 4, Pederson regular; 5, Huffman "virginal"; 6, pediatric regular; and 7, pediatric narrow.

The appropriate technique for cervical cytology testing is presented in Chapter 17. **Biopsy should be performed on any obvious lesions on the cervix or in the vagina.** An endometrial biopsy usually is performed with a flexible cannula or a Novak curette (see Chapter 14). Any purulence in the vagina or cervix should be cultured (see Chapter 16). **Testing for sexually transmitted diseases should be performed routinely in adolescents and young adults as recommended by the Centers for Disease Control and Prevention.**

After the speculum is removed and the pelvis palpated, lubrication is applied to the examination glove, and **one or two (the second and/or first) fingers are inserted gently into the vagina.** In general, in right-handed physicians, the right hand is inserted into the vagina and the left hand is used on the abdomen to provide counterpressure as the pelvic viscera are moved (Fig. 1.3). In patients with pelvic pain, a stepwise "functional pelvic exam"

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involves the sequential palpation of anatomic structures, including the pelvic floor, bladder, rectum, cervix, and cul-de-sac. These areas are assessed for tenderness and a specific source of pain. The vagina, its fornices, and the cervix are palpated carefully for any masses or irregularities. One or two fingers are placed gently into the posterior fornix so the uterus can be moved. With the abdominal hand in place, the uterus can usually be palpated just above the surface pubis. In this manner, the size, shape, mobility, contour, consistency, and position of the uterus are determined. The patient is asked to provide feedback about any areas of tenderness, and her facial expressions are observed during the examination.

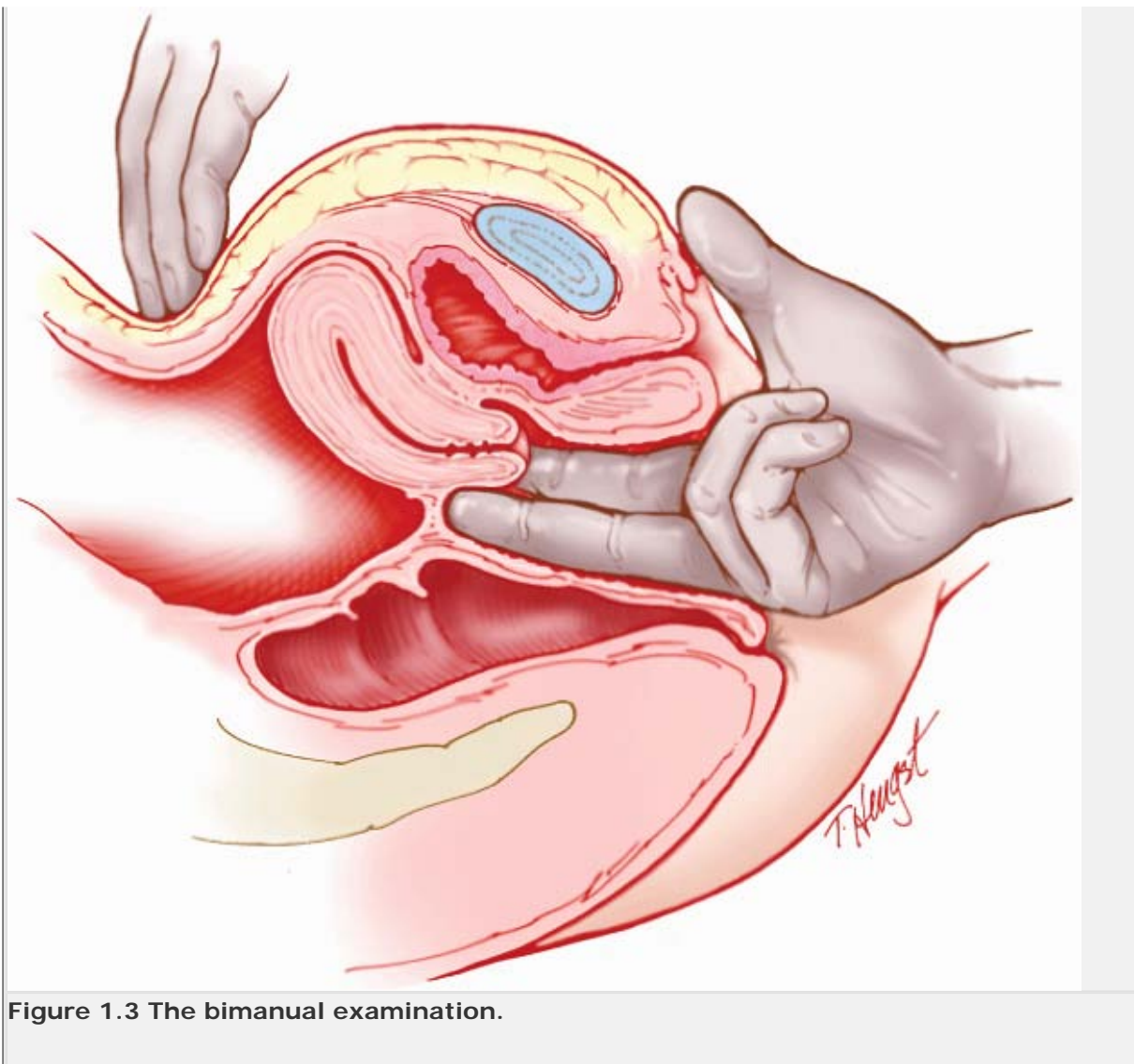


Figure 1.3 The bimanual examination.

The adnexa are then palpated gently on both sides, paying particular attention to any enlargements. Again, the size, shape, mobility, and consistency of any adnexal structures should be carefully noted.

A digital rectal examination is suggested periodically in women 40 years of age and older (see American College of Obstetricians and Gynecologists guidelines, Chapter 8) and may be helpful in premenopausal women in whom there is any difficulty ascertaining the adnexal structures (Fig. 1.4). Rectovaginal examination should also be performed in these women to exclude the possibility of concurrent rectal disease (38). Stool testing for occult blood has been found to reduce colon cancer mortality for individuals older than age 50 (39). During rectal examination, the quality of the sphincter muscles, support of the pelvis, and evidence of masses such as hemorrhoids or lesions intrinsic to the rectum should be noted. Nodularity and tenderness within the rectovaginal septum suggests endometriosis; nodularity may also suggest the spread of an intra-abdominal malignancy such as ovarian cancer.

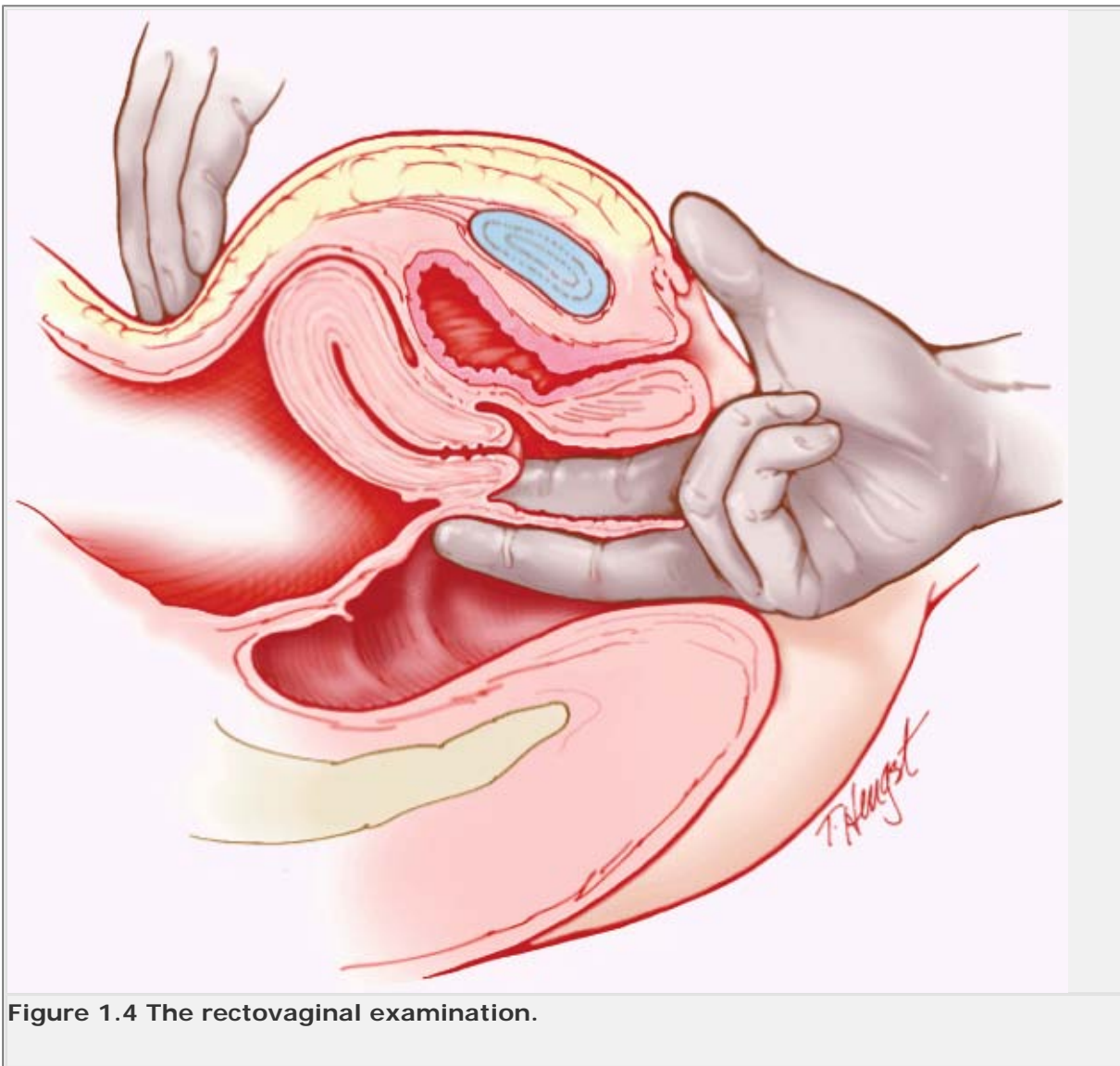


Figure 1.4 The rectovaginal examination.

At the completion of the physical examination, the patient should be informed of the findings. When the results of the examination are normal, the patient can be reassured accordingly. When there is a possible abnormality, the patient should be informed immediately; this discussion should take place after the examination with the patient clothed. A plan to evaluate the findings should be outlined briefly and in clear, understandable language. The implications and timing of any proposed procedure (e. g., biopsy) should be discussed, and the patient should be informed when the results of any tests will be available.

Pediatric Patients

A careful examination is indicated when a child presents with genital symptoms such as itching, discharge, burning with urination, or bleeding. The examiner should be familiar with the normal appearance of the prepubertal genitalia. The normal unestrogenized hymenal ring and vestibule can appear mildly erythematous. The technique of examination is different from that used for examining an adult and may need to be tailored to the individual child based on her age, size, and comfort with the examiner.

A speculum examination should not be performed in a prepubertal child in the office. A young child can usually be examined best in a "frog leg" position on the examining table.

Some very young girls (toddlers or infants) do best when held in their mother's arms. Sometimes, the mother can be positioned, clothed, on the examination table (feet in stirrups, head of table elevated) with the child on her lap, the child's legs straddling her mother's legs. The knee-chest position may also be helpful for the examination (40). The child who is relaxed and warned about touching will usually tolerate the examination satisfactorily. An otoscope can be used to examine the distal vagina if indicated.

Some children who have been abused, who have had particularly traumatic previous examinations, or who are unable to allow an examination may need to be examined under anesthesia, although a gentle office examination should almost always be attempted first. If the child has had bleeding and no obvious cause of bleeding is visible externally or within the distal vagina, an examination under anesthesia is indicated to visualize the vagina and cervix completely. A hysteroscope, cytoscope, or other endoscopic instrument can be used to provide magnification and light source for this examination, which should be performed with anesthesia.

Adolescent Patients

A pelvic examination may be less revealing in an adolescent than in an older woman, particularly if it is the patient's first examination or if it takes place on an emergency basis. **An adolescent who presents with excessive bleeding should have a pelvic examination if she has had intercourse, if the results of a pregnancy test are positive, if she has abdominal pain, if she is markedly anemic, or if she is bleeding heavily enough to compromise hemodynamic stability.** The pelvic examination occasionally may be deferred in young teenagers who have a classic history of irregular cycles soon after menarche, who have normal hematocrit levels, who deny sexual activity, and who will reliably return for follow-up. A pelvic examination may be deferred in adolescents who present to the office requesting oral contraceptives before the initiation of intercourse, or at the patient's request, even if she has had intercourse. Newer testing methods using DNA amplification techniques allow noninvasive urine testing for gonorrhea and chlamydia (41).

Other diagnostic techniques (such as pelvic ultrasound) can substitute for or supplement an inadequate examination. However, an examination is usually required when there is a question of pelvic pain, genital anomaly, pregnancy-related condition, or possibility of pelvic infection. **The keys to a successful examination in an adolescent lie in earning the patient's trust, explaining the components of her examination, performing only the essential components, and using a very careful and gentle technique.** It is helpful

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to ascertain whether the patient has had a previous pelvic examination, how she perceived the experience, and what she has heard about a pelvic examination from her mother or friends.

Before a first pelvic examination is performed, a brief explanation of the planned examination (which may or may not need to include a speculum), instruction in relaxation techniques, and the use of lidocaine jelly as a lubricant can be helpful. The patient should be encouraged to participate in the examination by voluntary relaxation of the introital muscles or by using a mirror if she wishes. If significant trauma is suspected or the patient finds the examination too painful and is truly unable to cooperate, an examination under anesthesia may occasionally be necessary. The risks of general anesthesia must be weighed against the value of information that would be obtained by the examination.

Confidentiality is an important issue in adolescent health care. A number of medical organizations, including the American Medical Association, the American Academy of Pediatrics, and the American College of Obstetrics and Gynecologists, have endorsed adolescents' rights to confidential medical care. Particularly with regard to issues as sensitive

as sexual activity, it is critical that the adolescent be interviewed alone, without a parent in the room. The patient should be asked if she has engaged in sexual intercourse, if she used any method of contraception, and if she feels there is any possibility of pregnancy.

Follow-up

Arrangements should be made for the ongoing care of patients, regardless of their health status. Patients with no evidence of disease should be counseled regarding health behaviors and the need for routine care. For those with signs and symptoms of a medical disorder, further assessments and a treatment plan should be discussed. The physician must determine whether he or she is equipped to treat a particular problem or whether the patient should be directed to another health professional, either in obstetrics and gynecology or another specialty, and how that care should be coordinated. If the physician believes it is necessary to refer the patient elsewhere for care, the patient should be reassured that this measure is being undertaken in her best interests and that continuity of care will be ensured.

Summary

The management of patients' gynecologic symptoms, as well as abnormal findings and signs detected during examination, requires the full use of a physician's skills and knowledge. Physicians are challenged to practice the art of medicine in a manner that leads to effective alliances with their patients. The value of skilled medical history-taking cannot be overemphasized. **Physicians should listen carefully to what patients are saying about the nature and severity of their symptoms.** They also should listen to what patients may not be expressing: their fears, anxieties, and personal experiences that lead them to react in a certain manner when faced with what is often, to them, a crisis (such as the diagnosis of an abnormality on examination, laboratory testing, or pelvic imaging).

Physicians should supplement their formal education and clinical experience by constantly striving for new information. To meet the challenges posed by the complexities of patient care, physicians must learn to practice evidence-based medicine, based on the very latest data of highest quality. Computers have made the world of information management accessible to both physicians and patients. Physicians need to search the medical literature to acquire knowledge that can be applied, using the art of medicine, to patient care to maintain health, alleviate suffering, and manage and cure disease.

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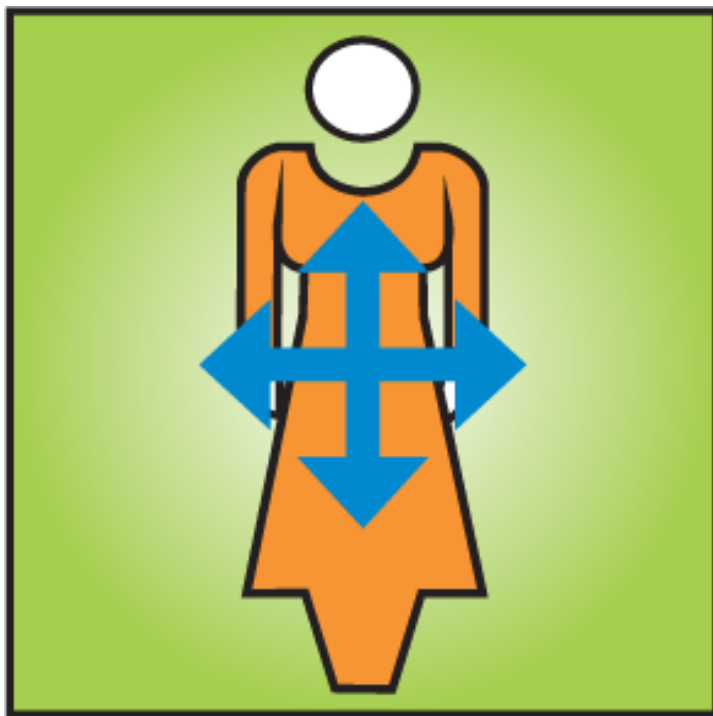
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2

Principles of Patient Care

Joanna M. Cain



- **The right to privacy prohibits a physician from revealing information regarding the patient unless the patient waives that privilege.**
- **Exceptions from the Healthcare Insurance Portability and Accountability Act (HIPAA) requirement to obtain patient authorization to share health information include areas such as patient treatment, payment, operations (quality improvement,**

quality assurance, education), disclosure to public health officials and health oversight agencies, and legal requirements.

- **Informed consent is a process whereby the physician educates the patient about the medical condition, explores her values, and informs her about the risks and benefits of treatment and reasonable medical alternatives.**
- **The concept of autonomy should not allow a patient's wishes to take precedence over good medical judgment.**
- **For children, parents are the surrogate decision makers, except in circumstances in which the decision is life threatening and might not be the choice a child would make later, when adult beliefs and values are formed.**
- **Research on the outcomes of care provided by gynecologists or affected adversely by the current system for financing health care (financial aspects, quality-of-life measures, survival, morbidity, and mortality) will allow the discipline to have a voice in determining choices for women's health care.**

The practice of gynecology, as with all branches of medicine, is based on ethical principles that guide patient care. These principles and concepts create a framework for ethical decision making that applies to all aspects of practice:

- **Autonomy: a person's right to self-rule, to establish personal norms of conduct, and to choose a course of action based on a set of personal values and principles derived from them**
- **Beneficence: the obligation to promote the well-being of others**
- **Confidentiality: a person's right to decide how and to whom personal**

medical information will be communicated

- **Covenant: a binding agreement between two or more parties for the performance of some action**
- **Fiduciary Relationship: a relationship founded on faith and trust**
- **Informed Consent: the patient's acceptance of a medical intervention after adequate disclosure of the nature of the procedure, its risks and benefits, and alternatives**
- **Justice: the right of individuals to claim what is due them based on certain personal properties or characteristics**
- **Maleficence: the act of committing harm (*Nonmaleficence* obliges one to avoid doing harm)**

Patient and Physician

Health care providers fulfill a basic need—to preserve and advance the health of human beings. Despite the challenges imposed by the commercial aspects of the current medical environment, for most physicians, the practice of medicine remains very much a “*calling*,” a giving of oneself to the greater good. Although much of medicine is contractual in nature, it cannot be understood in only those terms: “*The kind of minimalism that a contractualist understanding of the professional relationship encourages produces a professional too grudging, too calculating, too lacking in spontaneity, too quickly exhausted to go the second mile with his patients along the road of their distress*” (1). There is a relationship between physician and patient that extends beyond a contract and assumes the elements of a fiduciary relationship—a covenant between parties. **The physician, having knowledge about the elements of health care, assumes a trust relationship with the patient whereby her interests are held paramount. Both the patient and the physician have rights and responsibilities in this relationship, and both are rewarded when those rights and responsibilities are upheld. Confidentiality and informed consent are two expressions of that trust or covenantal relationship.**

Confidentiality

The patient seeking assistance from a health professional has the right to be assured that the information exchanged during that interaction is private. Privacy is essential to the trust relationship between doctor and patient. Discussions are privileged information. **The right to privacy prohibits a physician from revealing information regarding the patient unless the patient waives that privilege.** Privileged information belongs to the patient except when it impinges on the legal and ethical rights of institutions and society at large, regardless of the setting. In a court situation, for example, physicians cannot reveal information about their patients unless the patient waives that privilege. If privilege is waived, the physician may not withhold such testimony.

The privilege of privacy must be maintained even when it does not seem intrinsically obvious. A patient's family, friend, or spiritual guide, for example, has no right to medical information regarding the patient unless the patient specifically approves it, except if the patient is unable to provide that guidance because of their medical circumstance. In that circumstance, health providers must exercise their judgment based on their assessment of

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the involvement of that particular person with the patient's health. This may seem obvious but often can be overlooked, such as when a health care giver receives a call from a concerned relative inquiring about the status of a patient. The response may be a natural attempt to reassure and inform a caring individual about the patient's status. However, for her own reasons, the patient may not want certain individuals informed of her medical condition. Thus, confidentiality has been breached. It is wise to ask patients about who may be involved in decision making and who may be informed about their status. **If a health care giver is unclear of the patient's wishes regarding the person requesting information, the reply should indicate that the patient's permission is necessary before discussing her status. Finally, when trying to contact patients for follow-up of medical findings, it is never appropriate to reveal the reason to an individual other than the patient.**

Record Keeping

Health care professionals are part of a record-keeping organization. Those records are used for multiple purposes in medicine and are a valuable tool in patient care. Unfortunately, there is an increasing tendency for ancillary organizations to collect, maintain, and disclose information about individuals with whom they have no direct connection (2). Given the present lack of universal and nondiscriminatory access to

health insurance in the United States, physicians must be aware of this practice and its ramifications. Patients sign a document, often without understanding its meaning, upon registering with a health care institution or insurance plan. That document waives the patient's privilege to suppress access and gives insurers, and often other health care providers who request it, access to the medical record. The consequences of such disclosure for patients can be significant in terms of insurance coverage and potential job discrimination (3). This concern must be weighed against the need for all health care providers involved with an individual to be informed about past or present diseases or activities that may interfere with or complicate management. The use of illegal drugs, a positive human immunodeficiency virus (HIV) test result, and even a history of cancer or psychiatric illness are all exceptionally important to health care providers in evaluating individual patients. When revealed to outside institutions, however, these factors may affect the patient's ability to obtain medical care, insurance, or even credit. **Everything that is written in a patient's record should be important to the medical care of that patient, and extrinsic information should be avoided.** Furthermore, it is appropriate for physicians to discuss with patients the nature of medical records and their release to other parties so that patients can make an informed choice about such release.

The Healthcare Insurance Portability and Accountability Act (HIPAA), instituted in April 2003, has imposed additional requirements for access to patient records for clinical research as well as guidelines for protecting electronic medical records. Although the intent of the act was laudable, the extent to which privacy will be improved is unknown, and the potential harm to the public from failure to do critical database research because of its costly requirements may be greater than any benefit. The considerable confusion and misunderstanding of the rules associated with the act also can potentially harm patients. The exceptions from the requirement to obtain patient authorization to share health information include areas such as patient treatment, payment, operations (quality improvement, quality assurance, and education), disclosure to public health officials and health oversight agencies, and legal requirements (4). One widely misunderstood feature of the act was whether protected health information could be sent via fax or e-mail or mail to other treating physicians (which is allowed) (5). It is important that researchers understand the influence of these rules in all settings; preplanning for clinical database research when the patient first enters the office or institution will make this critical research possible (6). **The security of medical records, therefore, is a concern not just for individual patients and physicians but also for health systems and researchers.**

Legal Issues

The privilege of patients to keep their records or medical information private can be superseded by the needs of society, but only in rare circumstances. The classic legal decision quoted for the needs of others superseding individual patient rights is that of *Tarasoff v. Regents of the University of California* (7). That decision establishes that the special relationship between a patient and doctor may support affirmative duties for the benefit of third persons. It requires disclosure if "*necessary to avert danger to others*" but still in a fashion "*that would preserve the privacy of the patient to the fullest extent compatible with the prevention of the threatened danger.*" This principle also is compatible with the various codes of ethics that allow physicians to reveal information to protect the welfare of the individual or the community. In other words, "the protective privilege ends where the public peril begins" (7).

Legislation can also override individual privilege. The most frequent example is the recording of births and deaths, which is the responsibility of physicians. Various diseases are required to be reported depending on state law (e.g., HIV status may or may not be reportable in individual states, whereas acquired immunodeficiency syndrome [AIDS] is reportable in all states). Reporting injuries caused by lethal weapons, rapes, and battering (e.g., elder and child abuse) is mandatory in some states and not others. The regulations for the reporting of these conditions are codified by law and can be obtained from the state health department. These laws are designed to protect the individual's privacy as much as possible while still serving the public interest. Particularly in the realm of abuse, physicians have a complex ethical role regardless of the law. Victims of abuse, for example, must feel supported and assured that the violent act they have survived will not make a difference in how they are treated as people. Their sense of vulnerability and their actual vulnerability may be so great that reporting an incident may increase their risk for medical harm. Despite the laws, physicians also have an ethical responsibility protect the patient's best interest, and weighing that ethical responsibility can be difficult.

Informed Consent

Informed consent is a process that involves an exchange of information directed toward reaching mutual understanding and informed decision making. Ideally, informed consent should be the practical manifestation of respect for patient preferences (autonomy) (8,9). Unfortunately, an act of informed consent is often misunderstood as procurement of a signature on a document. Furthermore, the intent of the individual involved in the consent process often is the protection of

the physicians from liability. Nothing could be further from either the legal or ethical meaning of this concept.

Informed consent is a conversation between physician and patient that teaches the patient about the medical condition, explores her values, and informs her about the reasonable medical alternatives. Informed consent is an interactive discussion in which one participant has greater knowledge about medical information and the other participant has greater knowledge about that individual's value system and circumstances affected by the information. This process does not require an arduous lecture on the medical condition or extensive examination of the patient's psyche. It does require adjustment of the information to the educational level of the patient and respectful elicitation of concerns and questions. It also requires acknowledgment of the various fears and concerns of both parties. Fear that the information may frighten patients, fear of hearing the information by the patient, lack of ability to comprehend technical information, and inability to express that lack are among the many barriers facing physicians and patients engaging in this conversation. Communication skills are part of the art of medicine, and observation of good role models, practice, and positive motivation can help to instill this ability in physicians (10).

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Autonomy

Informed consent arises from the concept of autonomy. Pellegrino (11) defines an autonomous person as "one who, in his thoughts, work, and actions, is able to follow those norms he chooses as his own without external constraints or coercion by others." This definition contains the essence of what health care providers must consider as informed consent. The choice to receive or refuse medical care must be in concert with the patient's values and freely chosen, and the options must be considered in light of the patient's values.

Autonomy is not respect for a patient's wishes against good medical judgment. Consider the example of a patient with inoperable, advanced-stage cervical cancer who demands surgery and refuses radiation therapy. The physician's ethical obligation is to seek the best for the patient's survival (beneficence) and avoid the harm (nonmaleficence) of surgery, even though that is what the patient wishes. Although physicians are not obligated to offer treatment that is of no benefit, the patient does have the right to refuse treatment if it does not fit into her values. Thus, this patient could refuse treatment for her cervical cancer, but she does not have the right to be given any treatment she wishes.

Surrogate Decision Makers

If the ability to make choices is diminished by extreme youth, mental processing difficulties, extreme medical illness, or loss of awareness, surrogate decision making may be required. In all circumstances, the surrogate must make every attempt to act as the patient would have acted (12). The hierarchy of surrogate decision makers is specified by statutory law in each state and differs slightly from state to state. For adults, the first surrogate decision maker is a court-appointed guardian if one exists and second is a durable power of attorney, followed by relatives by degree of presumed familiarity (e.g., spouse, adult children, parents).

For children, parents are the surrogate decision makers, except in circumstances in which the decision is life threatening and might not be the choice a child would make later, when adult beliefs and values are formed.

The classic example of this is the Jehovah's Witness parents who refuse life-saving transfusions for their child (13). Although this case is the extreme, it illustrates that the basic principle outlined for surrogate decision making should also apply to parents. Bias that influences decision making (in protection of parental social status, income, or systems of beliefs) needs to be considered by physicians because the potential conflict may lead parents to decisions that are not in the best interest of the child. If there is a conflicting bias that does not allow decisions to be made in the best interest of the child or that involves a medical threat to a child, legal action to establish guardianship (normally through a child protective agency by the courts) may be necessary. This action can destroy not only the patient (child)–physician relationship but also the parent–physician relationship. It also may affect the long-term health and well-being of the child, who must return to the care of the parents. Such decisions should be made only after all attempts to educate, clarify, and find alternatives have been exhausted.

The legal age at which adolescents may make their own decisions regarding their health care varies by state (14). However, there is a growing trend to increase the participation of adolescents who are capable of decision making in decisions about their health care. Because minors often have developed a value system and the capacity to make informed choices, their ability to be involved in decisions should be assessed individually rather than relying solely on the age criteria of the law and their parents' views.

A unique area for consideration of informed consent is in the international context, either providing care or conducting clinical research in foreign settings or caring for individuals from other countries who have widely differing viewpoints regarding individual informed consent. For example, if the prevailing standard for decision making by a woman is that her closest male

relative makes it for her, how is that standard accommodated

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within our present autonomy-based system? In international research, these issues have presented major concerns when women were assigned to placebo or treatment groups and consent was accepted from male relatives (15). Furthermore, the coercive effect of access to health care through clinical trials when no other access to health care is available creates real questions about the validity and freedom of choice for participants in these studies (16). Guidelines for limiting coercion and ensuring the ability to choose participation in research are being developed for international research. When caring for patients from certain cultures and foreign countries in daily practice, however, it is important to recognize that these issues exist in a microcosm. Ensuring that the patient can make the choice herself (or freely chooses to have a relative make it for her) remains an important element of informed consent between individual physicians and patients.

Beneficence and Nonmaleficence

The principles of beneficence and nonmaleficence are the basis of medical care—the “to do good and no harm” of Hippocrates. However, these issues are often clouded by other decision makers, consultants, family members, and sometimes financial constraints or conflicts of interests. Of all the principles of good medical care, benefit is the one that continually must be reassessed. Simple questions often have no answers. What is the medical indication? How does the proposed therapy address this issue? How much will this treatment benefit the patient? How much will it extend the patient's life? Furthermore, when confronted with multiple medical problems and consultants, physicians should ask how much treatment will be of benefit given all the patient's problems (e.g., failing kidneys, progressive cardiomyopathy, HIV-positive status, and respiratory failure) rather than necessarily attempting intubation and respiratory support to treat the immediate problem.

The benefit or futility of the treatment, along with quality-of-life considerations, should be considered in all aspects of patient care. It is best to weigh all of the relevant issues in a systematic fashion. Some systematic approaches depend on a sequential gathering of all the pertinent information in four domains: medical indications (benefit and harm), patient preferences (autonomy), quality of life, and contextual issues (justice) (8). Other approaches identify decision makers, followed by facts, and then ethical principles. It is important for physicians to select an ethical model of analysis with which to practice so that, when faced with troubling and complex decisions, a system is available to help clarify the issues.

Medical Futility

The essence of good medical care is to attempt to be as clear as possible about the outcomes of the proposed interventions. If the proposed intervention (e.g., continued respiratory support or initiating support) has a very low or highly unlikely chance of success, intervention might be considered futile. Physicians have no obligation to continue or initiate therapies of no benefit (17). The decision to withdraw or withhold care, however, is one that must be accompanied by an effort to ensure that the patient or her surrogate decision maker is educated about the decision and agrees with it. Other issues, such as family concerns, can and should modify decisions if the overall well-being of the patient and of the family is best served. For example, waiting (within reason) to withdraw life support may be appropriate to allow a family to reach consensus or a distant family member to see the patient for a last time.

Quality of Life

Quality of life is a much used, often unclear term. In the care of patients, quality of life is the effect of therapy on the patient's experience of living based on her perspective. It is perilous and wholly speculative to assume that physicians know what quality of life represents for a particular patient judging from a personal reaction. It is instructive, however, to attempt to guess what it means and then seek the patient's perspective. The

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results may be surprising. For example, when offered a new drug for ovarian cancer, a patient might prefer to decline the treatment because the side effects may not be acceptable even when there may be a reasonable chance that her life may be slightly prolonged. In some instances, the physician may not believe that further treatment is justified but the patient finds joy and fulfillment in preserving her existence as long as possible.

Controversy exists regarding whether currently available quality-of-life measurement systems will provide information to help patients make decisions (18). Information from quality-of-life studies might be judged by criteria that include whether the measured aspects of the patient's life were based on the patient's views or the physician's clinical experience (19). Informing patients of the experiences of others who have had alternative treatments may help in their decision making, but it is never a substitute for the individual patient's decisions.

Professional Relations

Conflict of Interest

All professionals have multiple interests that affect their decisions. Contractual and covenantal relationships between physician and patient are intertwined and complicated by health care payers and colleagues, which create considerable pressure. The conflict with financial considerations directly influences how patients' lives are affected, often without their consent. Rennie (20) described that pressure eloquently: *"Instead of receiving more respect (for more responsibility), physicians feel they are being increasingly questioned, challenged, and sued. Looking after a patient seems less and less a compact between two people and more a match in which increasing numbers of spectators claim the right to interfere and referee."* An honest response to this environment is for the physician to attempt to protect his or her efforts by assuming that the physician–patient relationship is contractual, and only contractual, in nature. This allocation of responsibility and authority for the contract precludes the need for the covenant between the physician and patient. For example, a preexisting contract, insurance, relationship with a particular hospital system, or managed-care plan may discourage referral to a more knowledgeable specialist, removing the physician's responsibility. Thus, the contract seems to establish the extent of the physician–patient relationship. All health care providers must decide whether they will practice within a covenantal or contractual relationship and whether the relationship they develop remains true to this decision. In either setting, a reasonable perception of that relationship is "one that allows clients as much freedom as possible to determine how their lives are affected as is reasonably warranted on the basis of their ability to make decisions" (21).

Health Care Payers

An insurance coverage plan may demand that physicians assume the role of gatekeeper and administrator. Patients can be penalized for a lack of knowledge about their future desires or needs and the lack of alternatives to address the changes in those needs. Patients are equally penalized when they develop costly medical conditions that would not be covered if they moved from plan to plan. These situations often place the physician in the position of being the arbiter of patients' coverage rather than acting as an advocate and adviser. It is an untenable position for physicians because they often cannot change the conditions or structure of the plan but are made to be the administrators of it.

In an effort to improve physician compliance with and interest in decreasing costs, intense financial conflicts of interest can be brought to bear on

physicians by health care plans or health care systems. If a physician's profile on costs or referral is too high, he or she might be excluded from the plan, thus decreasing his or her

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ability to earn a living or to provide care to certain patients with whom a relationship has developed. Conversely, a physician may receive a greater salary or bonus if the plan makes more money. The ability to earn a living and to see patients in the future is dependent on maintaining relationships with various plans and other physicians. These are compelling loyalties and conflicts that cannot be ignored (22,23,24).

These conflicts are substantially different from those of fee-for-service plans, although the ultimate effect on the patient can be the same. In fee-for-service plans, financial gain may result in failure to refer a patient, or referral is restricted to those cases in which the financial gain is derived by return referral of other patients (25). Patients who have poor insurance coverage may be referred differentially. Patients may be unaware of these underlying conflicts of interest, a situation that elevates conflict of interest to an ethical problem. A patient has a right to know what her plan covers, to whom she is being referred and why, and the credentials of those to whom she is referred. The reality is that health care providers make many decisions under the pressure of multiple conflicts of interest. Physicians are potentially caught between self-interest and professional integrity. Whether it is blatant lying about indications for a procedure to receive reimbursement or a more subtle persuasion to sign up patients for a certain protocol because of points earned for a study group, the outcome for individuals' and society's relationship with health care providers is damaged by failure to recognize and specifically address conflicts of interest that impede decision making (26). **Focusing clearly on the priority of the patient's best interest and responsibly rejecting choices that compromise the patient's needs are ethical requirements.**

Institutions, third-party payers, and legislatures have avoided accountability for revealing conflicts of interest to those to whom they offer services. The restrictions of health care plans are never placed in a position as equally prominent as the coverage. The coverage choices can be quite arbitrary, and there is rarely an easily accessible and usable system for challenging them. Whole health systems or options may or may not be covered, but their presence or absence is obscured in the information given to patients. The social and financial conflicts of interest of these payers can directly affect the setting and nature of the relationship between physician and patient. To deal with ambiguous and sometimes capricious decision making, revelation of the conflicts of interest and accountability for choices should be demanded by physicians and patients (27).

Legal Problems

Abuses of the system (e.g., referral for financial gain) have led to proposals and legislation, often referred to as Stark I and II, affecting physicians' ability to send patients to local laboratories and facilities in which they have a potential for financial gain. Although there have been clearly documented abuses, the same legislation would affect rural clinics and laboratories in which the sole source of financial support is rural physicians. States vary on the statutory legislation regarding this issue. Regardless of the laws, however, it is ethically required that financial conflicts of interest are revealed to patients (28,29,30,31).

Another abuse of the physician–patient relationship caused by financial conflicts of interest is fraudulent Medicare and Medicaid billings. This activity resulted in the Fraud and Abuse Act of 1987 (42 U.S.C. at 1320a–7b), which prohibits any individual or entity making false claims or soliciting or receiving any remuneration in cash or any kind, directly or indirectly, overtly or covertly, to induce a referral. Indictments under these laws are felonies, with steep fines, jail sentences, and loss of the license to practice medicine. Physicians should be aware of the legal ramifications of their referral and billing practices (26,32).

Harassment

The goal of medicine is excellence in the care of patients and, often, research and education that will advance the practice of medicine. Thus, everyone involved in the process should be able to pursue the common goal on equal footing and without

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harassment that interferes with employees' or colleagues' ability to work or be equally promoted in that environment. Every office and institution must have written policies on discrimination and sexual harassment that detail inappropriate behavior and state specific steps to be taken to correct an inappropriate situation. The legal sanction for this right is encoded in both statutory law through the Civil Rights Act of 1964 [42 U.S.C.A. at 2000e–2000e–17 (West 1981 and Supp. 1988)] and reinforced with judicial action (case or precedent law) by state and U.S. Supreme Court decisions. In particular, charges of sexual harassment can be raised as a result of unwelcome sexual conduct or a hostile workplace (such as areas of medicine that have been known for antifeminist attitudes in the past). As stated in one legal case, “a female does not assume the risk of harassment by voluntarily entering an abusive, antifemale environment” (*Barbetta v. Chemlawn Service Co.*, 669 F. Supp. 569, W.D.N.Y., 1989). The environment must change; it is not acceptable to expect men or women to adapt because “*they knew what it would be like.*” The tension in

the legal debate regarding harassment (sexual, racial, disability) always hinges on the weight of protection of free speech and the right of the individual to equality and a nonhostile work environment.

Stress Management

There is little doubt that the day-to-day stress of practicing medicine is significant. Besides the acknowledged stress of the time pressures and responsibility of medicine, the current health care environment has had a detrimental effect on physicians' job security, with concurrent health risks (33). Stress takes a toll not only on cardiac function (34) but also on the practice of medicine and life outside of medicine (35).

Responding to stress through drug or alcohol abuse increases overall health and marital problems and decreases effectiveness in practice. In a long-term prospective study of medical students, individuals with high-risk (e.g., volatile, argumentative, aggressive) temperaments have been shown to have a high rate of premature death (particularly before 55 years of age) (36). **Adequate sleep, reasonable working hours, exercise, and nutritional balance are directly related to decreases in psychological distress (37).** Simple relaxation training has been shown to decrease gastroesophageal reflux in response to stress (38).

The pace that physicians maintain has a seductive quality that can easily mask the need for stress reduction by means of good health practices, exercise, and relaxation training. The answer to increased stress is not to work harder and extract the time to work harder from the relaxing and enjoyable pursuits that exist outside medicine. The outcome of that strategy (in terms of optimal psychological and physical functioning) is in neither the physician's nor the patient's best interest. Both the welfare of the patient and the welfare of the physician are enhanced by a planned strategy of good health practices and relaxation. Furthermore, such a strategy is important to all members of the health care team. By providing such leadership, physicians can contribute to a better work and health care environment for everyone.

Society and Medicine

Justice

Some of the ethical and legal problems in the practice of gynecology relate to the fair and equitable distribution of burdens and benefits. How benefits are distributed is a matter of great debate. There are various methods of proposed distribution:

Equal shares (everyone has the same number of health care dollars per year)

-
- Need (only those people who need health care get the dollars)
-
- Queuing (the first in line for a transplant gets it)

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-
- Merit (those with more serious illnesses receive special benefits)
-
- Contribution (those who have paid more into their health care fund get more health care)

Each of these principles could be appropriate as a measure of just allocation of health care dollars, but each will affect individual patients in different ways. Only recently has just distribution become a major issue in health care. The principles of justice apply only when the resource is desired or beneficial and to some extent scarce (39).

The traditional approach to medicine has been for practitioners to accept the intense focus on the individual patient. However, the current changes in medicine will alter the focus from the patient to a population (40)—*"in the emerging medicine, the presenting patient, more than ever before, will be a representative of a class, and the science that makes possible the care of the patient will refer prominently to the population from which that patient comes."* Physicians are increasingly bound by accumulating outcomes data (population statistics) to modify the treatment of an individual in view of the larger population statistics. If, for example, the outcome of liver transplantation is only 20% successful in a patient with a certain set of medical problems, that transplant may instead be offered to someone who has an 85% chance of success. Theoretically, the former individual might have a successful transplant and the procedure might fail in the latter, but population statistics have been used to allocate this scarce resource. The benefit has been measured by statistics that predict success, not by other forms of justice allocation by need, queuing, merit, or contribution. This approach represents a major change in the traditional dedication of health care to the benefits of individual patients. With scarce resources, the overall benefits for all patients are considered in conjunction with the individual benefits for one patient.

There has always been an inequity in the distribution of health care access and resources. This inequity has not been seen by many health care providers who

do not care for those patients who are unable to gain access, such as those who lack transportation or live in rural areas or where limits are imposed by lack of health care providers, time, and financial resources. Social discrimination sometimes leads to inequity of distribution of health care. Minorities are less likely to see private physicians or specialists, regardless of their income or source of health care funding (41,42,43). Thus, health care is rationed by default.

Health care providers must shift the paradigm from the absolute "do everything possible for this patient" to the proportionate "do everything reasonable for all patients" (8). To reform the health care system requires not just judicial, legislative, or business mandates but also attention to the other social components that can pose obstacles to efforts to expand health care beyond a focus on individual patients.

Health Care Reform

The tension between understanding health as an inherently individual matter (in which the receipt of health care is critical to individual well-being) and as a communal resource (in which distribution of well-being throughout society is the goal) underpins much of the political and social debate surrounding health care reform (44). The questions of health care reform are twofold: 1) What is the proper balance between individual and collective good? and 2) Who will pay for basic health care? Because much of health care reform requires balancing competing goals, legislation to achieve reform should specifically address how this balance can be achieved. The role of government should be as follows:

- Regulating access of individuals to health care
- Regulating potential harms to the public health (e.g., smoking, pollution, drug use)
- Promoting health practices of benefit to large populations (e.g., immunization, fluoridation of water)

In the present health system structure in the United States, health care payers, not

individual providers, often make decisions regarding both the amount and distribution of resources. The health insurance industry determines what are "reasonable and customary" charges and what will be covered. The government decides (often with intense special-interest pressure) what Medicare and Medicaid will cover (45,46,47). These decisions directly affect patient care. For that reason, health care providers cannot ethically remain silent when the health and well-being of their individual patients and their communities are adversely affected by health care reform decisions.

The significant growth of uninsured individuals and uncompensated care in the United States reflects a threat to the health of women that should be of concern to all. The United States "*is one of the few industrialized nations in the world that does not guarantee access to health care for its population*" (48). The direct health consequences for women are significant and contribute to death and disability in our population. The burden of the shifted costs is falling more heavily on certain institutions, and the private community is providing less care for this population. The "*implicit assumption of the United States health care system is that poor, uninsured persons who become ill can obtain free or discounted care*" (49). There is, in fact, no more margin of funds that can be shifted to cover the cost of this care. The choice to provide access only to those who can afford it through wealth or through insurance coverage as our means of health care allocation is antithetical to the professional oaths and ethical standards of medicine. Health care providers should assess proposed reforms—or lack of action toward reform—in light of the needs of their community and their individual patients. Criteria should be established for judging proposals for health care reform, and physicians should add their voice to the debate on access (50,5152).

Research on the outcomes of care provided by gynecologists or affected adversely by the current system for financing health care (financial aspects, quality-of-life measures, survival, morbidity, and mortality) will allow the discipline to have a voice in determining choices for women's health care.

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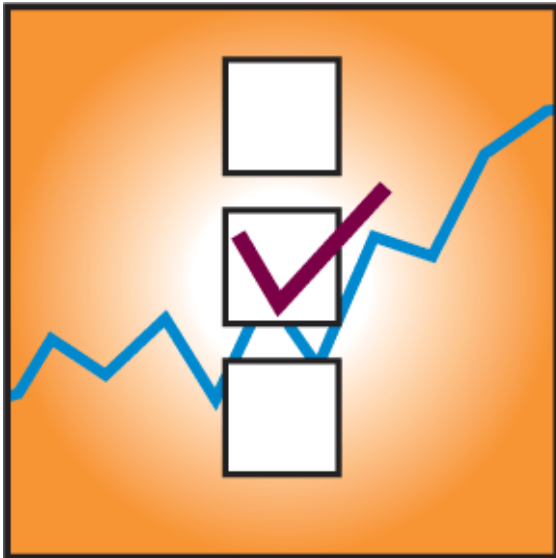
3

Quality Assessment, Performance Improvement, and Patient Safety

Joseph C. Gambone

Robert C. Reiter

Paul A. Gluck



- **The emphasis on health care quality has been stimulated by the need to control costs.**
- **The principles of quality assessment in health care have evolved from traditional retrospective review.**
- **Newer methods to assess and improve the delivery of health care services involve prospective measurement of the processes of care to improve health outcomes.**
- **The discovery of the extent of preventable medical error has led to an emphasis on improving patient safety.**
- **Disclosure of medical error is now recommended by professional societies**

and mandated by accrediting agencies.

The need to maintain or increase the quality and safety of health care while controlling costs is stimulating a great deal of interest and activity in quality assessment and performance improvement. Several reports from the Institute of Medicine (IOM), on medical error (1) and on health care quality (2), have generated considerable public interest and concern about the overall quality of health care in the United States and the high estimated number of preventable deaths caused by medical errors. Although some of the conclusions of these reports have been questioned, the findings raise fundamental and disturbing questions about health care quality and safety in the United States.

Health Care Costs

The annual per capita expenditure for health care (in constant dollars) in the United States has risen steadily from about \$950 in 1970 to more than \$6,000 in 2004 (averaging about

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12% increases per year). Although efforts in the 1990s to "manage" care and its costs were reasonably successful in slowing increases in annual health care premiums, they have recently been returning to double digits (Table 3.1). According to a Kaiser Foundation survey, the cost of health insurance increased by 59% during the 5-year period from 2000 to 2005, whereas workers wages increased by only 12%. Currently, annual United States per capita expenditure for health care delivery is estimated to exceed \$6,500. The "political" failure and public distrust of 1990s-style managed care has resulted in predictions of its demise despite well-documented economic success (3). Before the mid-1990s, much of the increase in health care costs had been shifted from individuals to state and federal governments and to employers. More recently, however, employers have been setting limits on their contributions to health care benefits and shifting more of the increased costs to their employees. Some employers have even discontinued benefits. Currently, the United States spends more on health care (approaching 16% of gross domestic product) than on education and defense combined.

Table 3.1 Annual Health Care Premium Increases (%) in the United States

Year	%	Year	%
1990	17	1998	3.7
1991	18	1999	7.8
1992	12	2000	9.4
1993	10	2001	10.2
1994	6.5	2002	14.3
1995	-1	2003	13.9
1996	2	2004	11.2
1997	4		

Despite this enormous outlay of resources, there is concern about the overall quality of health care (2,4). The health status of U.S. residents (in terms of life expectancy, neonatal mortality, and rates of illness and disability) is poorer than that of people living in most European and Scandinavian countries, the United Kingdom, Japan, and Canada, although these countries spend far less per capita on health care. Quality improvement programs in other industries have shown that management methods can both increase quality and reduce

costs. Because of concerns about quality, cost, and safety, patients, as well as private and public third-party payers, are demanding ongoing quality assessment and performance improvement programs in health care delivery systems.

Traditional Quality Assessment

Until recently, the medical profession has focused its efforts largely on assessing and improving the quality of health services through internal, self-imposed, retrospective peer review. Examples of such mechanisms are morbidity and mortality (M&M) review conferences, medical society-sponsored and state-legislated peer-review programs, surgical case reviews (tissue committees), and the specialty board-certification processes. These programs review adverse occurrences retrospectively (e.g., assessment of medical and surgical complications and review of misdiagnoses). **Although useful as part of the peer-review process, these "quality assurance" or QA programs are not aimed at prevention of errors and are not designed to assess and improve the effectiveness of health care services and procedures** (5).

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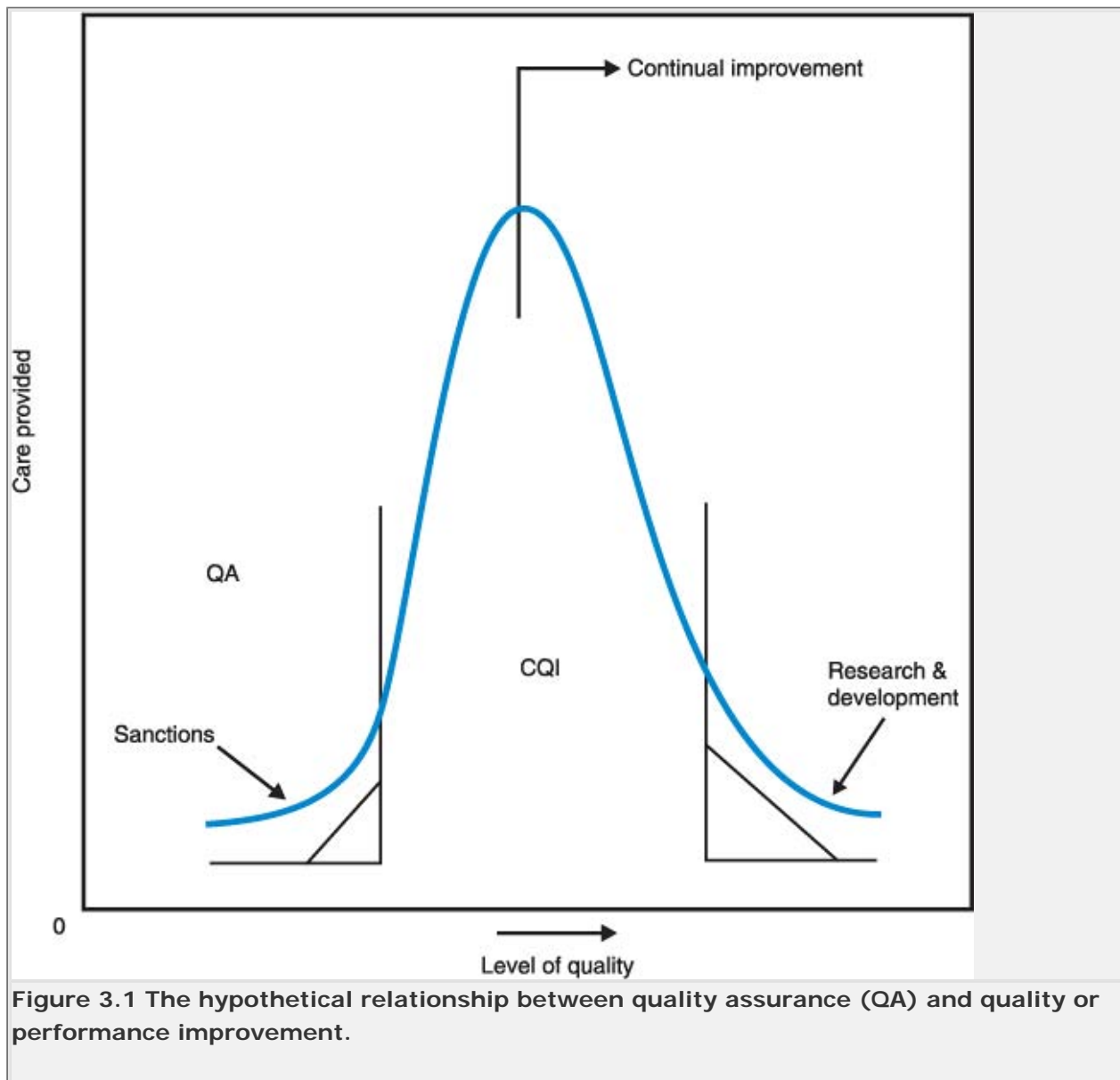


Figure 3.1 The hypothetical relationship between quality assurance (QA) and quality or performance improvement.

The differences between traditional QA programs and newer performance

improvement and quality management programs, such as continuous quality improvement (CQI) or total quality management (TQM), are presented in Figure 3.1. Quality Assessment programs are designed to identify and eliminate the small percentage of substandard care represented on the left side of the normal curve (the "bad apple" approach). Most "standard" care occurs in the middle of the curve, however, and is the focus of newer programs like CQI. Such programs are designed to study prospectively the processes of care based on need and to improve outcomes by the reduction of unintended variation (6). The right side of the curve represents state-of-the-art practice usually performed under protocols at universities and other large centers of excellence that are monitored by institutional review boards and national research groups such as the National Cancer Institute and the Gynecologic Oncology Group. As more emphasis is placed on quality management programs in health care, innovations should come from both traditional research and performance improvement efforts.

Quality management programs such as CQI, TQM, and performance improvement each have three essential elements (7):

- **To understand customers (patients, payers, and other clients) and to link that knowledge to the activities of the organization**
- **To mold the culture (beliefs and performance characteristics) of the organization through the deeds of leaders; to foster pride, enjoyment, collaboration, and scientific thinking**
- **To increase knowledge (of how to improve performance) continuously and to control variation (unintended and wasteful differences in performance) by scientific methods**

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Health care professionals often do not like to refer to health care services as *products* and to patients as *customers* or *consumers*. The older, paternalistic attitude (i.e., patients passively agreeing to health care procedures that were determined largely by health care providers) is being replaced by a more egalitarian view of patients as intelligent and informed consumers who should participate in their care (8). The consumerism movement in health care is predicated on the belief that health care services should conform to acceptable standards of quality, efficiency, and safety (9). This newer attitude may lead to improved communication and shared decision making (between patient and provider) and should alter the wasteful practice of "defensive medicine," which has been shown to increase health care costs significantly (10,11).

Principles of Quality Assessment

Quality means different things in different situations. The concept of quality in products (e.g., consumer goods and state-of-the-art machinery) is different than that of complex services (e.g., health care delivery to people). However, many of the principles of quality assessment and improvement that have been shown to improve the quality of consumer goods and services can also be applied to the evaluation and improvement of health services. There are certain principles of quality assessment that should be considered when attempting to measure and improve health care quality.

Efficacy, Effectiveness, and Efficiency

Efficacy and ***effectiveness*** are similar terms that are often used interchangeably to describe evaluations of outcomes of health care services and procedures. As defined by the IOM, ***efficacy*** refers to what an intervention or procedure can accomplish under ideal conditions and when applied to appropriate patients (12). ***Effectiveness*** refers to the actual performance in customary practice of an intervention or procedure.

An example of this difference is the theoretical success rate (***efficacy***) of oral contraception used for 1 year (99% successful at preventing pregnancy) versus the actual or ***use-rate*** effectiveness, usually reported to be 93% to 97%. Most health care decisions have been based on efficacy rates obtained from controlled clinical trials rather than the actual effectiveness of such decisions. One of the major challenges for quality assessment and management programs is to develop and use measurements that reflect the actual, or real-life, success rates of treatment options so that evidence-based decision making can replace authority-based decision making. Also, strategies need to be developed to improve patient compliance rates to increase the likelihood that the actual effectiveness is as close as possible to theoretical efficacy (13).

Efficiency describes the relative "waste" or resource use (complications and costs) of alternative effective interventions. To realize meaningful improvements in health services, health professionals and organizations must develop more efficient interventions (e. g., medical therapy or expectant management versus surgical treatment for abnormal bleeding) when appropriate. The goal of health care quality improvement is optimal value. ***Value*** is defined as quality divided by the cost, or as the quotient of outcomes (benefits) divided by resources used:

$$\text{Value} = \text{outcomes}/\text{resource use.}$$

Optimal versus Maximal Care

The assessment of the quality of health care depends on whether the goal of the system is to provide maximally effective or optimally effective care (14). Figure 3.2 shows a theoretical representation of the difference between maximally effective health care (Point B),

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in which every conceivable intervention is offered regardless of cost to those who can afford it, and optimally effective health care (Point A), in which resources are used in a manner that will provide the most good for as many people as possible. Maximized health care emphasizes individual intervention, whereas optimized care emphasizes public health care and prevention. When optimal health care becomes the goal of a health care system, conflicting individual and societal needs must be resolved.

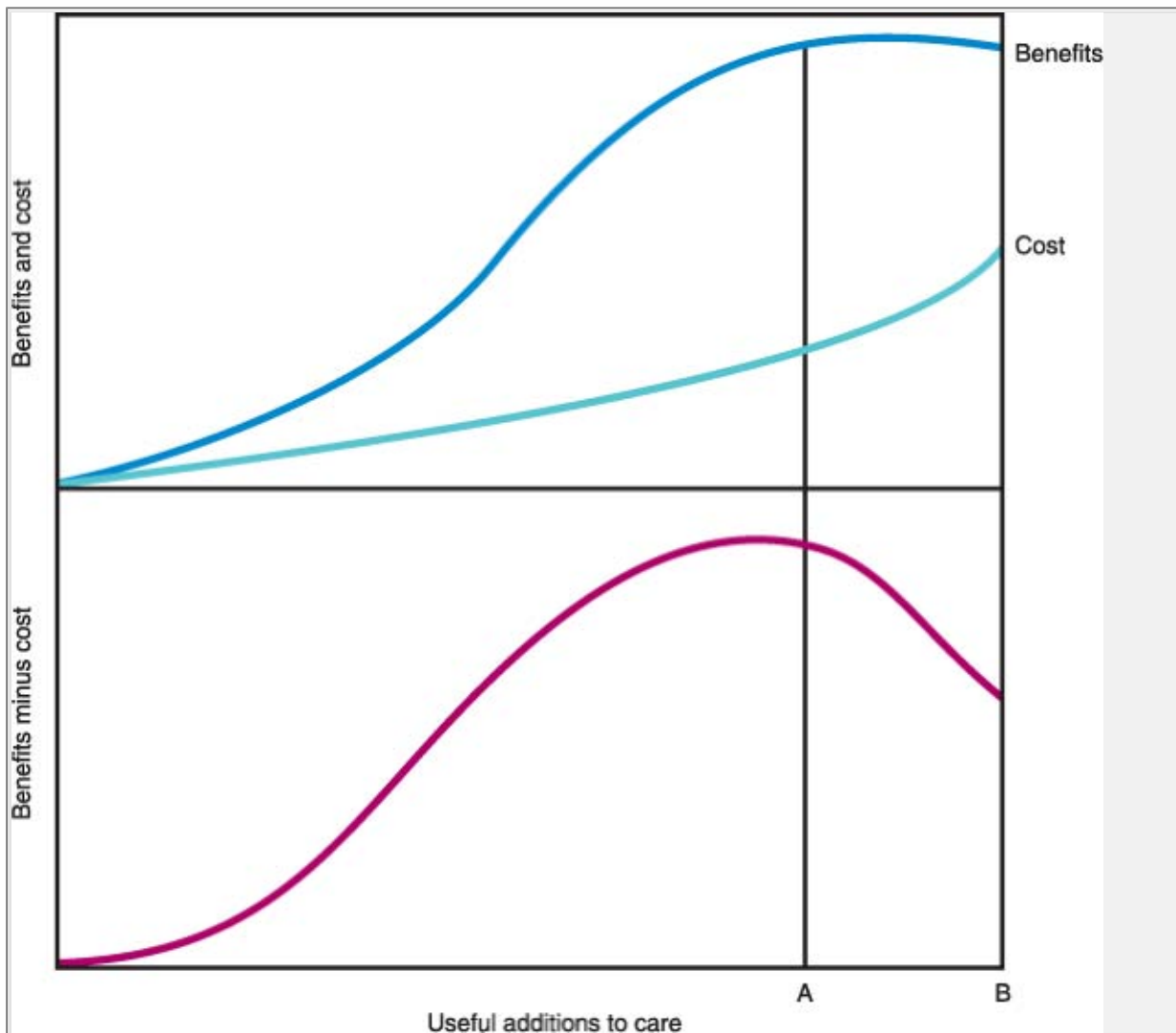


Figure 3.2 The “optimal” versus the “maximal” benefits and costs of medical treatments. On the *top panel*, the benefits to health and the costs of care are plotted. On the *bottom panel*, the cost is subtracted from the benefits, illustrating that after a certain point, additions of care may detract from the benefits. (From **Donabedian** A. The quality of care: how can it be assessed. *JAMA* 1988;260:1743–1748, with permission.)

Assessing Outcomes

A widely accepted system for assessing the quality of health care is based on the measurement of indicators of structure, process, and outcome (15). **Structure** includes the resources, equipment, and people who provide health care. **Process** is the method by which a procedure or course of action is executed. **Outcome** includes the complications, adverse events, and short-term results of interventions, as well as the patient's health status and health-related quality of life after treatment, which reflects the effectiveness of the intervention.

Evaluation of health care structure involves the assessment of the stable and tangible resources needed to provide care, such as safe and adequately sized operating rooms and properly functioning equipment. Other examples of structural elements include the aspects of the medical staff's qualifications, such as school accreditation, licensure, continuing

medical education credits, and specialty board certification. Although these elements form the foundation of a health care organization or system, there is a weak correlation between structural assessment and other measures of the quality of care, such as clinical outcomes (16). Therefore, many health-services researchers believe that organizations need to measure clinical outcomes directly (including not only death and short-term morbidity but also disability and health-related quality-of-life issues) if they hope to improve both the effectiveness and efficiency of health care delivery. Their research also emphasizes measurement of clinical or health outcomes that are defined as those that patients can experience and value without the interpretation of a health care provider. Examples of clinical or health outcomes and their corresponding intermediate or surrogate end points are presented in Table 3.2. **Ultimately, longevity and quality-of-life factors may be the only relevant outcomes of health care.**

Table 3.2 Clinical and Health Outcomes and Their Corresponding Intermediate or Surrogate Endpoints: Some Examples

<i>Clinical or Health Outcomes</i>	<i>Intermediate or Surrogate Endpoints</i>
Longevity	Dilated coronary arteries
Quality of life	Five-year survival rate
Take baby home	Pregnancy
Pain relief	Fewer adhesions
No transfusion	Less blood loss

Quality-of-Life Measurement

In the past, traditional quality-assessment programs have tended to focus on the assessment of short-term risks and the confirmation of pathologic diagnoses.

This effort has usually been limited to quantification of mortality and major morbidity—such as infection, blood transfusion, and the need to re-operate—that occurred while the patient was hospitalized and was verified by tissue diagnosis. Most standardized lists of clinical QA indicators are from the medical model of outcomes assessment. Although the importance of these kinds of indicators seems obvious, these indicators may have little or no relevance to the more fundamental question of actual effectiveness of a procedure in terms of preserving or enhancing quality of life. For example, if a patient with pelvic pain undergoes a hysterectomy for leiomyomata, experiences no short-term complications, and has a diagnosis that is confirmed histologically, the procedure may be considered successful from the standpoint of surgical risk management, short-term outcome, and histologic verification. However, if the patient continues to experience pain and has no improvement in the quality of her life, the surgery has been, in reality, unsuccessful. **Short-term risk indicators often have little or no bearing on whether the procedure actually works.**

Behavioral Model of Health Outcomes

Efforts to measure the success or the effectiveness of health care procedures in the United States are based on the traditional medical model in which a patient is evaluated for a symptom, diagnosed as having a condition, and treated for that

diagnosis. A procedure is usually considered successful if the diagnosis is confirmed.

Medicine has traditionally relied on short-term risk indicators and histologic confirmation because these measurements seem more objective and quantifiable.

Death and infection rates, blood loss, and rates of histologic verification can all be measured and expressed numerically. Crucial to the application of a more predictive behavioral model in clinical outcomes research are several statistically valid and reliable methods to measure health-related quality of life. Many measures have been developed and validated, but few are used in clinical practice (17).

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Using the **behavioral model** of effectiveness, the concept of **quality-adjusted life-years** (QALY) has been proposed to measure the benefit, in both quantity and quality of life, of a health care procedure (18). **The number of QALYs is determined by combining the extra years of life that a procedure offers with a validated measure of eight categories of disability and four measures of distress.** The use of this methodology allows standardized comparison of the cost of entirely different health care procedures. Despite its inadequacies, the medical model has been the standard, but now the behavioral model of outcomes is being incorporated increasingly into health care evaluation and research (19). Scales of health-related quality-of-life issues, called the *SF-36* and the *SF-12* (short form 36 and short form 12) based on the health-status tool derived from the RAND Medical Outcomes Survey, have been developed (20).

Performance Improvement

Most methods for the assessment of the quality of health care and the delivery of health services have been based on the premise that quality is the sole responsibility of the health care practitioner. Because the practitioner's technical skills, knowledge, and interpersonal interactions are the basis for quality of patient care and its delivery, many regulatory agencies (e.g., the Joint Commission on the Accreditation of Health Care Organizations [JCAHO]) and hospitals have created traditional QA models that focus mostly on the practitioner. However, many interacting forces determine quality of care, and the practitioner clearly does not deliver care in isolation. The delivery of health care requires the integration and management of many processes. The practitioner's ability to deliver care is influenced by the environment, the ability and skill of support staff, policies and procedures, facilities, governing processes, methods of work, and equipment and materials available, as well as innumerable patient variables, such as severity of illness, concurrent illness (comorbidity), and social support. Historically, QA efforts attempted to monitor these processes to document bad outcomes. However, this approach has not proved to be adequate in improving the quality of care (21). Regulatory agencies and hospitals are now focusing on the overall performance of health care organizations in terms of clinical or health outcomes.

Performance improvements in health care have been based on knowledge that physicians and other health care professionals acquired in medical and other professional schools. Improvements have been brought about by clinicians applying knowledge developed by discipline-specific experts (22). The recent national emphasis on health care reform is an indication that the past rate of improvements is not sufficient to meet the financial needs and expectations of society. Performance improvements in efficiency must be made at a faster pace because consumers are seeking greater value for and access to health care services. A theoretical basis for organizational change that promotes continuous improvement includes knowledge of a system, knowledge of variation, and the theory of knowledge (23,24).

Knowledge of a System

The first component of continuous performance improvement is knowledge of a system.

A system is defined as a network of interdependent components that work together to accomplish its aim. A system does not exist without an aim and is capable only of improving if there is a connection between the aim, the means of production, and the means of improving. An open system is one that permits continued access from outside the system. Because health care organizations are accountable to patients and to the community as a whole, they are considered open systems. The aim of an organization involves the integration of the knowledge of the social needs and the needs of patients.

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Knowledge of a system includes three components:

- **Customer knowledge**, derived by identifying the organization's customers and by understanding the measures they use to judge quality
- **How the organization provides its services**, which involves knowledge of processes or steps taken to deliver the service
- **How the organization improves**, which involves knowledge of the aim and identification of areas for improvement that are likely to have the greatest impact

Understanding the interrelationships between the aim, the customers, the primary areas for improvement, and the specific processes that can be improved is known as *systems thinking*. When a health care organization is focused on providing as many services as possible without consideration for the needs of the community and their customers, it will eventually fail to deliver quality services. **Proper perspective for customer needs and preferences gained through a process called *strategic planning* may even lead to a competitive advantage for a health care organization** (25).

Knowledge of Variation

Another element of continuous improvement is knowledge of variation. Variation is present in every aspect of our lives. Variation is inherent to everyone's behavior, learning styles, and ways of performing a task. Although the presence of variation, or uniqueness, can be considered a kind of quality, most services are judged on the basis of predictability and a low level of variation. When a service is thought to be of high quality, we expect it to be exactly the same each time, and if there is to be any variation, it must be an improvement.

To improve health products and services continually, it is necessary to know the customers, their needs, and how they judge the quality of health services. The processes by which health services are delivered must be understood and unintended variations reduced. If an organization is to improve and be innovative, it must plan changes that are based on knowledge of what can be better. Two types of variation found in production processes are those that occur by chance (common cause) and those due to assignable causes (special causes) (26). The ability to differentiate between these two types of variation is essential to making improvements in health care.

Clinicians regularly make decisions in their practices based on variation. For example, a physician making frequent rounds may note a change in a patient's temperature and may decide to treat or to observe the patient based on the temperature change and on experience (i.e., judgment). If the temperature variation is seen as special cause (i.e., infection), a decision may be made to prescribe an antibiotic. However, if the change or variation is interpreted as common-cause variation in temperature due to short-term, normal changes or chance, it may be ignored. If this happens often, the physician may alter the frequency of observation, thereby making an improvement to the monitoring process. Frequently, however, common-cause variation is not recognized in health care, and the variation is acted on prematurely, resulting in the overuse of resources and a lower quality of care (7). If the approach is to measure and change, too many costly changes might be made.

Learning how to respond appropriately to variation in health care processes is a major challenge. Understanding and controlling variation in health care services should be the main emphasis of quality management. The notion of controlling variation, however, causes concern and skepticism in many health care professionals. Physicians who fear any effort to control variation are worried about the loss of options and about restrictions on their judgment. As Berwick points out (7), however, "The (problem) is not considered, intentional variation, but rather unintended or misinterpreted variation in the work of

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health care. Unintended variation is stealing health care blind today. In controlling it, the health care system could potentially recover a bounty in wasted resources that would dwarf the puny rewards of cost-containment to date."

Variation in Utilization

One of the earliest and most compelling influences on modern health care quality assessment in the United States was a series of investigations that demonstrated a wide variation in the use of health care procedures (27). Although previous investigations had documented a twofold to fourfold difference in the rates of selected procedures both within the United States and between the United States and other industrialized countries, these variations usually were disregarded as secondary to population differences. However, a small-area analysis documented similar or even greater magnitudes of variation within small (25 to 50 miles) geographic regions that could not be explained by differences in patient characteristics or appropriate differences in standards of care (28).

Variations in utilization have now been analyzed for virtually all major surgical procedures, including hysterectomy and cesarean delivery (29,30). Also, variation in the performance of medical procedures, such as those used in the management of acute myocardial infarction and sepsis, has been identified (31). On the basis of these analyses, significant variation has been documented in utilization and in important outcomes such as complications, cost, and derived benefit (32). This type of analysis does not usually allow accurate assessment of which rate of utilization or outcome is appropriate. However, it can help to focus attention on the quality of health services and the complexities of using statistically valid methods to measure health care quality.

Variation in utilization of health care services can be categorized as follows:

- **Necessary and intended variation because of well-recognized patient differences, such as severity of illness, comorbidity, and legitimate patient preferences**
-

Acceptable but reducible variation because of uncertainty and lack of accurate information about outcomes

Unacceptable variation because of nonclinical factors, such as habitual differences in practice style, which are not grounded in knowledge or reason

Most of the differences in utilization rates of many health care procedures result from the last two categories.

Variation in Women's Health Care

Overall, the rate of inpatient surgery for women age 15 to 44 years is more than 3 times that of males, excluding vaginal deliveries. The most commonly performed major surgical procedure in the United States is cesarean delivery, with about one million procedures (one quarter of all births) performed annually in the United States. Rates of cesarean delivery vary by region, state, and small geographic areas. Overall, the rate of cesarean deliveries is 12% to 40%, and the national mean is about 23%. Comparative rates for the United Kingdom are 6% to 12%.

Hysterectomy is also a common inpatient surgical procedure in the United States. The total annual incidence of hysterectomy for all ages, all indications, and all institutions (federal and nonfederal) in the United States exceeds 500,000.

Hysterectomy rates in the southern and western United States are 50% to 75% higher than those in the Midwest and New England. A twofold to fivefold variation in utilization rates has been documented within states and small geographic areas within the United States (29). National rates in the United States are twice those in the United Kingdom and more than three times the rates in Sweden and Norway (33).

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Hysterectomy utilization in the United States varies by both provider and patient characteristics. Studies of utilization patterns have demonstrated that older physicians are more likely than younger physicians to recommend hysterectomy and that (when controlled for age) sex does not appear to influence hysterectomy decision making (34). With respect to patient variables, although hysterectomy utilization is similar among African-American women and white women (35,36), low income and low educational level are risk factors for hysterectomy (37). By 65 years of age, the prevalence of hysterectomy is 40% for women with a high school education and 20% for women with a college education.

Short-term outcomes of hysterectomy vary significantly by race. African-American women have a substantially higher relative risk (RR) for morbidity and in-hospital mortality (RR = 3.1) compared with age- and condition-matched white women (38). The reasons for this variation are not known. Quality management techniques are being applied to research in an attempt to eliminate these wasteful variations.

The Theory of Knowledge

The final component of knowledge for improvement is the theory of knowledge. **The theory of knowledge refers to the need for the application of a scientific method for improving performance.** One model for testing small-scale change is called the **Plan, Do, Study, Act (PDSA)** method (24). Unlike the ideal scientific method recommended for clinical trials, the PDSA method does not include a control group. Although randomized controlled trials

have been considered to be the best way to determine the value of health care interventions, they have two distinct disadvantages: they are expensive, and they tend to define the efficacy of an intervention such as a drug or a surgical procedure. Because efficacy is the way an intervention works under ideal conditions, compared with effectiveness, which is the way an intervention works in everyday practice, health services researchers now recognize that it may not be possible to generalize about an intervention's effectiveness based on its efficacy as measured in a randomized trial. Also, it is too expensive to perform randomized trials in all situations in which the effectiveness of health care services needs to be improved.

This continuous improvement model has found application in health care performance improvement (24). The PDSA cycle has been further modified as *FOCUS-PDCA*: **F**ind a process, **O**rganize a team, **C**larify the process, **U**nderstand the variation, and **S**elect an improvement (**FOCUS**). In this model, the **P** represents the need to *plan* an improvement by first identifying a change that might lead to improvement and then testing the change on a small scale. During this phase, who will do what, when the change will occur, and how the change will be communicated to those who will be affected are detailed. The **D** stands for *doing* or implementing the plan (change to the process) and collecting the data. The **C** stands for *checking* the data to determine whether the change to the process represents an improvement, and the **A** stands for *acting* or incorporating the change into the process if it is found to be an improvement. A new cycle with another change is started if an improvement was not recognized.

Health care organizations are seeking efficient ways to optimize their delivery of health care and to improve services. The notion that high-quality health care automatically means high cost is no longer accepted without question. At a time when many businesses have transformed themselves by using newer methods of quality management, enabling them to deliver high-quality goods and services at reasonable costs, health care professionals and organizations are beginning to test these improvement methods in medical and surgical practice.

Newer Methods for Improving Performance

Health services researchers and clinicians are beginning to develop and validate newer methods for the measurement and improvement of health care quality. For example, there is a need to make valid comparisons of quality between divergent populations and to

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correlate clinical performance with measurable processes of care. The goal of a new branch of investigation called **clinical evaluative** or **outcomes sciences** is to obtain valid measures of relevant outcomes that are correlated with measurable processes of care so that changes in process can be identified and initiated, thereby improving outcomes. This discipline incorporates methodologies from divergent areas such as epidemiology, clinical research, management, engineering, economics, and behavioral sciences.

Statistical adjustments are used to allow clinically dissimilar populations, such as high-risk and low-risk patients and those with complicated and uncomplicated conditions, to be compared. This procedure is called *case-mix adjustment* and controls for severity of illness and comorbidity (39,40). Outcomes that are assessed include traditional (medical model) measures, such as complications and adverse occurrences, as well as newer, well-validated measures of satisfaction, health, and functional status.

Concurrently, the processes of care are assessed. This assessment includes measurement of resources used during an episode of care (e.g., supplies, medications, specialized personnel) and practice parameters (e.g., physician orders and nursing practices).

Measurement of the processes and outcomes of health care can be prohibitively

expensive if this measurement is not integrated into the daily clinical care. For this reason, another goal of clinical quality outcomes research is to develop and incorporate methods of quality assessment into routine practice. This mechanism could be accomplished, for example, by using the SF-36 as a standard nursing intake form at the time of admission.

Analytic methods in clinical outcomes science rely heavily on multivariate statistics and iterative outcomes databases to provide valid correlations between measurable (and changeable) processes and outcomes. However, the mere identification of process changes that would improve outcomes does not ensure that they will, in fact, be used. For this reason, process and outcomes data must be linked to methods that will allow this information to be incorporated into clinical and operational decision making if they are to change behavior and improve outcomes. These analyses must be readily available both geographically and temporally at the point of care (the place and time that the decision is made) if they are to improve outcomes.

One approach to QA, performance improvement, and medical decision making that has been recommended (the PREPARED system) uses a checklist to analyze the value of a health care procedure before it is performed (9,41). The purpose is to review sequentially the critical data categories of information, each represented by a letter in the word **PREPARED**, that should be used to determine the most appropriate course of action or choice (42):

Procedure	the course of action being considered
Reason	the indication or rationale
Expectation	the chances of benefit and failure
Preferences	patient-centered priorities (utilities) affecting choice
Alternatives	other reasonable options
Risks	the potential for harm from procedures
Expenses	all direct and indirect costs
Decision	fully informed collaborative choice

Standardized procedural analysis using this sequenced checklist has been shown to improve health care decision making by increasing patient satisfaction and self-efficacy, thereby facilitating patient choice. It has the potential to improve the assessment of the quality and appropriateness of both provider and patient decision making.

Outcomes Research and Evidence-Based Clinical Guidelines

In the past, clinical practice guidelines or parameters have been largely derived by expert opinion and consensus. A major goal of clinical outcomes science is to allow for the development of guidelines based on actual measured outcomes that could self-adjust based on performance and newer methods of diagnosis and treatment. **One such process for incorporating outcomes data into clinical practice is the *critical pathway–case management method* (43).** In this method, consensus practice parameters for a given condition (e. g., management of preterm labor) are initially developed by a multidisciplinary team consisting of all professional, allied, and support services involved in the care of the target population. **This list of parameters is called a *critical path* or *clinical map*. The critical path details all laboratory, dietary, consultative, medical, teaching, and nursing activities that are thought to be necessary to obtain specific clinical outcomes. Outcomes of care, as well as variations from the “path,” are monitored and collected continuously.**

Positive and negative outcomes are analyzed and correlated with variances from the critical pathway. These data are then returned to the multidisciplinary team, which recommends changes in the entire path based on the outcomes and variance analyses.

In one pilot study of a critical pathway method for cesarean delivery, length of stay and cost were reduced by 13% and 14%, respectively. Additionally, five of seven measurements of satisfaction, including quality of care, were improved, and health status was unchanged (43). A relatively new federal government agency, the Agency for Healthcare Research and Quality (AHRQ), formerly known as the Agency for Health Care Policy and Research (AHCPR), is responsible for funding developmental efforts, collecting information about clinical care guidelines, and disseminating information. AHRQ has provided a comprehensive repository of available evidence-based clinical guidelines through an outstanding searchable Web site (<http://www.guidelines.gov>).

Patient Safety and Medical Error

The term "patient safety" was first used by the American Society of Anesthesiologists in 1984 to refer to the avoidance of medical error. Patient safety has been identified by the IOM as one of the most important dimensions of health care QA and performance improvement. **According to a recent report from the IOM, it is estimated that between 44,000 and 98,000 preventable deaths may be due to medical error (1). Although there continues to be controversy about the validity of methods used in these analyses, critics admit that even if the actual number of preventable deaths from error is much smaller than estimated, efforts should be made to eliminate as many as possible.**

Patient safety has its roots in traditional risk management (RM) but there are important conceptual differences between the two (Fig. 3.3). **Risk management is retrospective and is focused on individual outliers. It is also outcomes oriented and addresses significant adverse (sentinel) events. The goals of RM include sanctions for substandard providers with far less attention to finding systems-oriented improvements that could prevent recurrent medical errors. Patient safety initiatives are prospective, interdisciplinary, and focused on health care process in addition to outcomes. They are designed to be nonpunitive and to recognize that most adverse outcomes result from systems deficiencies and not individual error. Therefore, system changes in the overall process of delivery of care are necessary to prevent future problems.** For example, when the wrong extremity is removed during a therapeutic amputation, RM efforts usually focus on legal liability issues, holding surgeons and operating room personnel accountable. Ideally, a patient safety initiative would study the entire process of care using a root-cause analysis approach (Fig. 3.4). All of the members of the health care team, from admission to discharge, would be involved to identify and implement preventive measures. This "going beyond blame" approach was a significant recommendation in the IOM report, and it is the approach that is commonly used in other industries, such as aviation safety (1). Process changes and improvements include such practices as having the

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patient and surgeon sign the correct extremity using indelible ink at the time of admission and sharing the responsibility during the process so that several individuals (operating room personnel, anesthesia personnel, and members of the surgical team) would verify that the correct extremity is prepared and eventually removed. This team accountability approach is now being applied in all specialties, including obstetrics and gynecology.

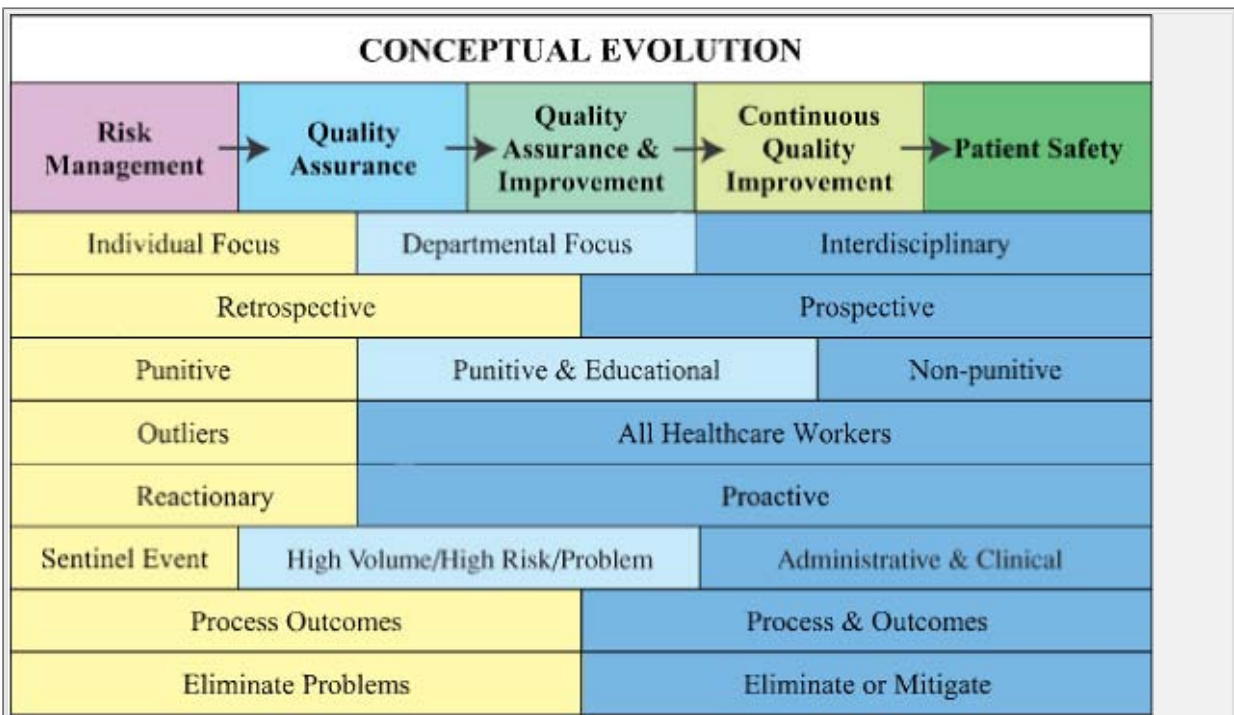


Figure 3.3 A conceptual evolution of the characteristics of risk management (RM), quality assurance (QA), continuous quality improvement (CQI), and patient safety.

JCAHO has been active and influential in the evolution of patient safety activities. Starting with an initial requirement that all significant (sentinel) events be reported, it now requires that root-cause analyses be used to investigate incidents, identify contributing factors, and improve the process of care (44). Starting with all JCAHO surveys performed after June 2001, the Joint Commission requires documented evidence that a health care organization being reviewed has invested in a "top-down" commitment to patient safety improvement.

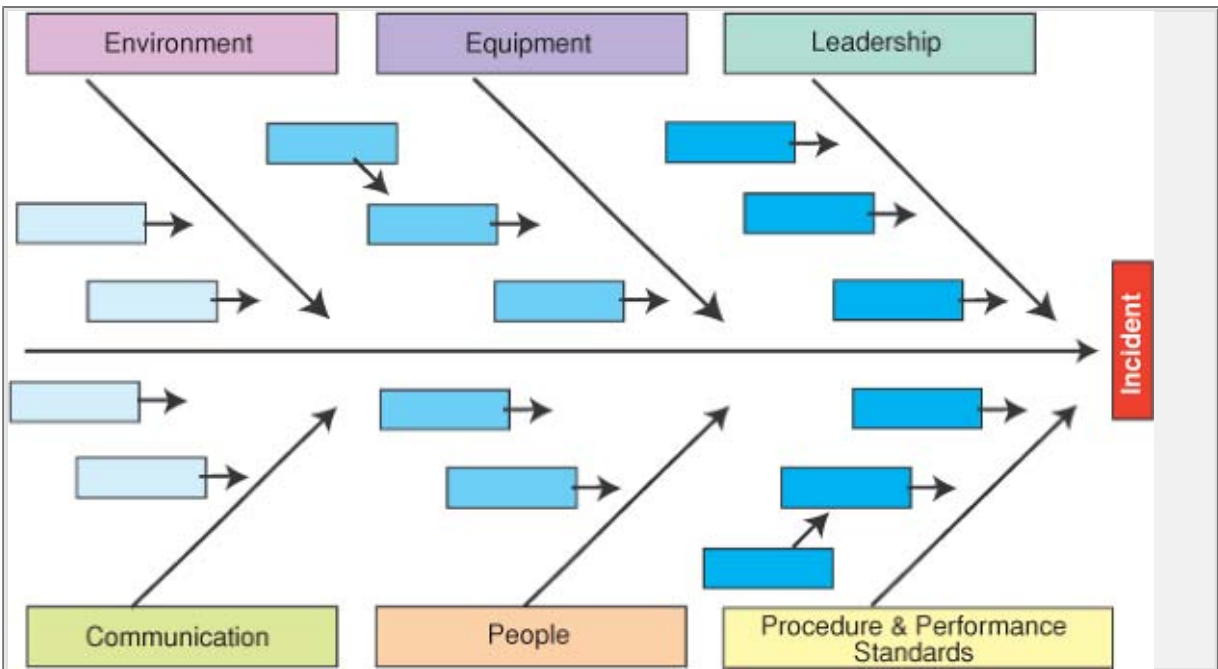


Figure 3.4 Root-cause(s) analysis: getting to the single or multiple causes of adverse outcomes.

Business and government are also interested in promoting patient safety activities. A business committee called the Leapfrog Group, representing the National Business Roundtable and corporations such as General Electric, General Motors, and Verizon, have announced that they will give purchasing preference to health care organizations that have at least the following three patient safety programs that have been shown to improve performance: (a) 24-hour, 7-days-per-week in-house coverage by intensive-care specialists; (b) computerized physician-order (CPOE) systems; and (c) referral to "centers of excellence" with documented best outcomes for high-risk procedures, such as cardiovascular and transplant surgeries. Properly designed computer systems, such as CPOE, can improve physician work flow and decrease serious medical errors by more than 50% and reduce adverse drug events by nearly 85%.

Leaders in health care assessment and performance improvement have recommended five principles to help make health systems safer:

- **Leadership in the organization should commit to patient safety to provide the necessary personnel and financial resources.**
- **System design should recognize human limitations. The noted health care improvement researcher, David Eddy, has stated that "the complexity of modern medicine exceeds the limitations of the unaided human mind." The one-person ("captain-of-the-ship") accountability of the past may actually lead to more errors in the current health care system.**
- **Working and training in teams can help deliver safer care and more dependable accountability.**
- **Training should emphasize the need to anticipate the unexpected.**
- **The organization should foster a learning environment for continual improvement of patient safety.**

Disclosure and Reporting of Medical Error

The official position of the National Patient Safety Foundation (NPSF) concerning the disclosure of medical errors when health care injury occurs is that the patient and the family or representative are entitled to a prompt explanation of how the injury occurred and its short- and long-term consequences. Patients should be informed that the factors involved in the injury will be investigated so that steps may be taken to reduce the likelihood of similar injury to other patients (<http://www.NPSF.org>). During the process of informing patients and their families about medical error, it is very important to listen to how they feel about what has happened, explain the events further when asked, and to empathize with the feelings that are expressed (45). Recent evidence suggests that proper disclosure of unintentional medical error may actually decrease lawsuits (46).

There is a growing consensus that there will need to be a nonpunitive reporting system to identify not only medical errors but also "near misses" and other hazards so that they may be corrected before the patient is harmed. The aviation industry is a prime example of how measures can be taken to improve safety. Operations are simplified

and standardized. Crew resource management empowers the most appropriate individual to correct a problem, even if that person is not the pilot. Simulators and team training are widely employed. The industry has a system, the airline safety reporting system, for reporting actual incidents and near misses. Furthermore, this system is confidential and

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separated from the Federal Aviation Agency (their main regulatory body) by the National Aviation and Space Agency.

AHRQ has stated that recognition and reporting of medical errors is an important component of quality assessment to improve patient safety. Currently AHRQ publishes case studies of medical error (including ob-gyn examples) on the World Wide Web at <http://www.webmm.ahrq.gov>.

Summary

Quality assessment and performance improvement activities are becoming increasingly important components of health care delivery. Although retrospective peer review and other QA efforts are still necessary, newer, prospectively focused methods to improve performance are being introduced. In the past, managing the cost of health care has been a major rationale for quality assessment and performance improvement programs. Recently, however, concerns about patient safety and deficiencies in quality have been prompted by several IOM reports (1,2). The complexity of modern health care delivery now requires a multidisciplinary team approach to quality management and error reduction. **To improve health care quality and safety significantly, health care professionals need to move away from an atmosphere of blame and individual accountability to a more effective systems approach. This process should include appropriate disclosure and analysis of medical error that is focused on measurable performance improvement.**

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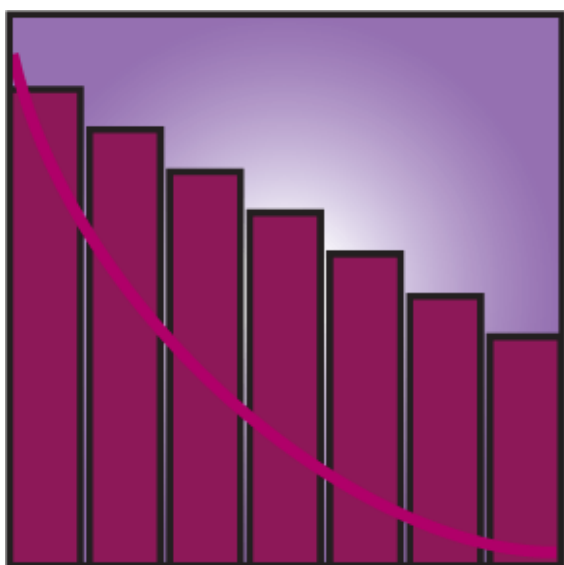
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4

Epidemiology for the Gynecologist

Daniel W. Cramer

Karen Loeb Lifford



- ***Epidemiology*** is the study of the occurrence of health events in human populations.
- ***Incidence*** is the rate of occurrence of new cases over a specified time, whereas ***prevalence*** is the existing number of cases at a point in time.
- ***Epidemiologic studies*** can be descriptive, including case series and cross-sectional studies, or analytic, including cohort studies, case-control studies,

and clinical trials. Analytic studies provide a higher level of evidence because they test a hypothesis about and measure an association between exposure and outcome.

•

Cohort studies measure the occurrence of a particular outcome among those who did or did not have a particular exposure (or treatment). *Attributable risk* is the difference between the occurrence measure in exposed versus unexposed, whereas the relative risk is the ratio between the two.

•

A *case-control study* assesses exposures among individuals with or without a particular disease or outcome of interest. The measure of the association is the exposure odds ratio, which approximates the relative risk.

•

Judging the *scientific validity* of an epidemiologic study requires addressing whether chance, bias, or confounding could have accounted for the findings.

•

Misclassification, as may occur from differential recall of the exposure, and *selection bias* may especially affect case-control studies, whereas *confounding* can occur in all types of analytic studies.

•

A *clinical trial* is a prospective cohort study to evaluate treatment for disease in humans with the key feature of randomization of the treatment assignment to minimize bias and confounding.

•

Dose response, *consistency*, and *biologic credibility* are three factors often used in judging whether an association between exposure and outcome represents cause and effect.

•

A *meta-analysis* is a formal method for assessing consistency and pooling results from several independent studies examining the same exposure (or treatment) and outcome and is a key tool of evidence-based medicine.

•

Reproductive epidemiology may include the domain of studies that address how reproductive events may affect common diseases in women and how

common exposures may affect reproductive diseases.

Epidemiology is the study of the occurrence of health events in human populations.

Studies typically thought of as epidemiologic in nature are those investigating how disease or death rates vary by age or nationality or how risk for a disease changes after a specific exposure. Epidemiologic concepts are much broader, however, and enter into the interpretation of almost all studies performed in humans. To critically read the gynecologic literature and practice evidence-based medicine today, physicians must have an increasingly sophisticated knowledge of epidemiologic concepts. In this context, it is important to be aware of the types of epidemiologic studies, their strengths and limits, and criteria for judging their validity. An understanding of the impact of common exposures on gynecologic diseases as well as the impact of gynecologic conditions on common diseases provides perspective on the scope of epidemiology in gynecology. Readers are urged to consult other resources for additional information, especially regarding some of the methodological aspects (1,2,3,4,5,6,78).

Gynecologic diseases have always been a major focus for epidemiologic research. Involvement of gynecologists in the design and interpretation of such studies can help ensure that the physiologic and clinical relevance of various associations are adequately discussed. Even if the gynecologist does not actually perform epidemiologic research, an understanding of epidemiologic principles allows for a more critical reading of the medical literature and sharpens the practice of preventive medicine in gynecology.

Study Designs

Epidemiologic studies may be broadly categorized as either *descriptive*, examining the distribution and frequency of disease, or *analytic*, examining the relationship between exposure and disease. The methodology of a study can affect the strength of the evidence it provides. Thus the U.S. Preventive Task Force created a framework by which the quality of evidence can be assessed (Table 4.1) (7).

Descriptive Studies

The two principal types of descriptive studies are **case series** and **cross-sectional studies**.

Case Reports or Series

Design

In a case report or case series, the characteristics of individuals who have a particular disease are described. Through the description of individual cases, hypotheses

about exposures and disease are developed that can then be further explored in analytic studies. For example, a link between oral contraceptives and thromboembolism was first suggested by case reports (2,3) and later confirmed in a case-control study (4). Occasionally, when case series describe the co-occurrence of rare exposures and rare diseases, they are compelling enough on their own to suggest a cause-and-effect relationship. Links between thalidomide and fetal limb reduction (5), the Dalkon shield intrauterine device and septic abortion (6), and sequential oral contraceptives and premenopausal endometrial cancer (8) emerged through case series that were persuasive enough to initiate public health action without the performance of formal epidemiologic studies. In general, however, just because members of a case series share a particular characteristic, one cannot assume that there is a cause-and-effect relationship. The quality of the information provided by a case report or series is evaluated by scrutinizing the details of the case selection. Investigators should strive to be sure that clear criteria exist for the definition of disease or study variables and that identification of cases was complete.

I.	Evidence obtained from at least one properly designed, randomized controlled trial.
II-1.	Evidence obtained from well-designed controlled trials without randomization.
II-2.	Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group.
II-3.	Evidence obtained from multiple time series with or without the intervention.
III.	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Incident cases, which are new cases identified after the study's start, are more likely to provide accurate information about factors related to the development of the condition under study. When case series extend over a long period, changes in the diagnosis or treatment of the condition may confuse objectives. The quality of the information (record-based or personal contact with the patient) and interobserver or reviewer reliability also needs to be assessed. Because a case series has no comparison group, statistical tests of association between the exposure and illness cannot be performed. However, careful assembly of a case series is the first step in performing a case-control study, which is the logical extension of a case series.

Yield

A case series does not usually yield any formal epidemiologic measures other than estimates of the frequency, or prevalence, of a particular characteristic among members of the case series. This is often referred to as the *incidence* of a particular characteristic among cases, but *prevalence* is usually the more appropriate term.

Cross-Sectional Studies

Design

Cross-sectional studies are larger in scope than case series and generally do not focus on a particular disease. Individuals are surveyed to provide a “snapshot” of health events in the population at a particular time. The U.S. Census Bureau counts the population by categories of age, sex, and ethnicity. The U.S. National Center for Health Statistics compiles a wide variety of data on the health of the population, such as occurrence of hospitalization for various conditions. State health departments are required to count the number of births and deaths annually in their population, and some maintain registries to count the number of individuals who have cancer.

Yield

Incidence is the rate of occurrence of new cases of diseases or conditions over a specific time. Cross-sectional studies often yield incidence rates in which births, new disease cases, or deaths are counted annually for a specified census region and divided by the population size to yield events per population per year. The rate is usually multiplied by a base (1,000, 10,000, or 100,000) to give numbers that can more easily be tabulated. Incidence is an important concept in epidemiology and is often used to calculate other measures of disease frequency, such as prevalence and lifetime risk.

Age-specific incidence refers to the number of new events occurring in 5- or 10-year age groups per year. Because of marked differences by age for most illnesses, age-specific incidence rates are the best way to describe event occurrence in a population. If the incidence rate is not specified with regard to age, it is described as “crude” or unadjusted.

Prevalence is the existing number of cases at a specific point in time. Prevalence is another measure frequently developed from cross-sectional studies. For example, in 1988, the Family Growth Survey Branch of the National Center for Health Statistics interviewed a sample of married couples and found the prevalence of infertility among married women younger than

45 years of age in the United States to be about 8.0% (9). The National Health and Nutrition Examination Survey (NHANES) is a series of population-based surveys designed to collect information on the health and nutrition of the U.S. population. From this study we have learned that the seroprevalence of herpes simplex virus-2 in the United States is increasing, from 16.7% in NHANES-II (midpoint 1978) to 21.7% in NHANES-III (midpoint 1991) (10). Because prevalence measures disease status in a population rather than events occurring over time, prevalence is a proportion, not a rate.

Although cross-sectional studies are primarily descriptive, they may contribute information on the cause of a disease by showing how that disease varies by age, sex, race, or geography. In *ecologic studies*, disease rates in various populations are correlated with other population characteristics (e.g., endometrial cancer rates worldwide are positively correlated with per capita fat consumption and negatively correlated with cereal and grain consumption) (11). Such observations are valuable in suggesting topics for analytic studies or supporting the consistency of an association.

Analytic Studies

The purpose of an analytic epidemiologic study is to test a hypothesis about and to measure an association between exposure (or treatment) and disease occurrence (or prevention) (Fig. 4.1). **Analytic studies may be subdivided into *experimental studies* and *nonexperimental, or observational, studies*.**

In *experimental studies*, such as clinical trials, the investigator assigns exposure; thus these studies cannot involve exposures known, or strongly suspected, to be harmful. The goal of an experimental study is to confirm that the observed outcome is due to the assigned exposure. Thus features these studies should include are randomization (in which participants are randomly assigned to exposures), measures to ensure unbiased assessment of outcome, and analysis of all participants based on assigned exposure (an "intention to treat" analysis). Many exposures may not be amenable to an experimental design, either because the exposure is rare or suspected to have harmful effects.

***Observational analytic studies* include cohort and case-control studies and take advantage of "natural experiments" in which exposure is not assigned by the investigator; rather, individuals do or do not have a particular disease and have or have not had an exposure of potential interest.**

Observational Studies

Cohort Studies

Design

A cohort is a group of people who have some factor in common. In the context of a survival analysis, the cohort begins with a population that is 100% well (or alive) at a particular time and is followed over time to calculate the percentage of the

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cohort still well (or alive) at later times. **Survival analysis describes mortality after disease (i.e., cancer patients who died within 5 years) but can be adapted to other events (e.g., the percentage of women who continue to menstruate after 50 years of age or the percentage of infertile women who conceive after therapy).**

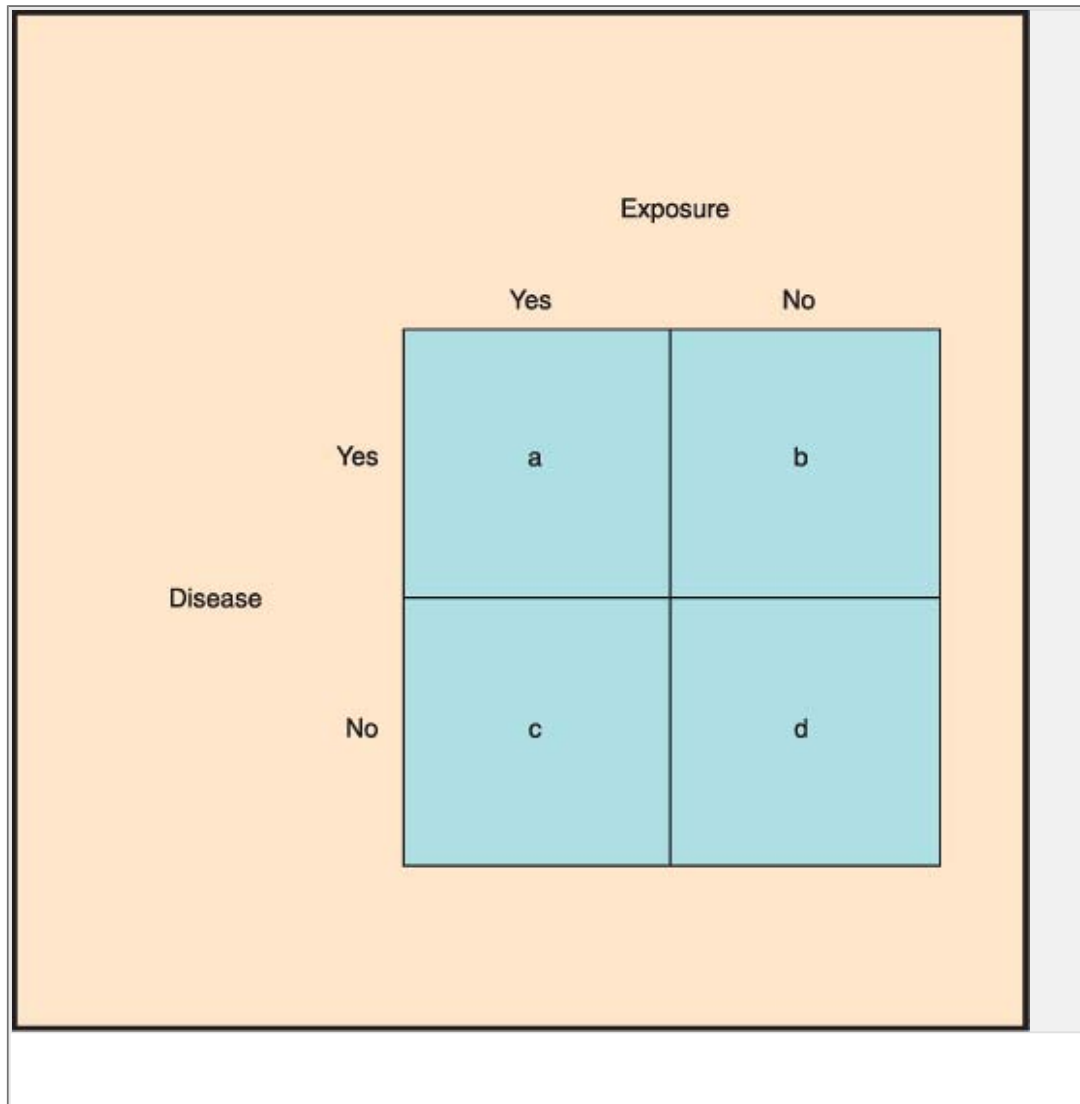


Figure 4.1 The essential design of an epidemiologic study showing the relationship between exposure (or treatment) and disease.

Other types of cohorts are defined by subsets of a population who are, have been, or may in the future be exposed to factors hypothesized to influence the occurrence of a given disease.

The exposed and nonexposed subjects are observed long enough to generate *person-years* as the denominator for incidence or mortality rates in exposed and nonexposed subsets (Fig. 4.2).

Cohort studies are also called ***follow-up*** or ***longitudinal studies***. Cohort studies may be **prospective**, meaning that the exposure is identified before outcome, or **retrospective**, in which the exposure and outcome have already occurred when the study is begun. For example, studies of radiation and subsequent cancer are often based on records of patients who received radiation therapy many years previously. Medical records and death certificates are used to determine whether a second cancer occurred after the radiation therapy.

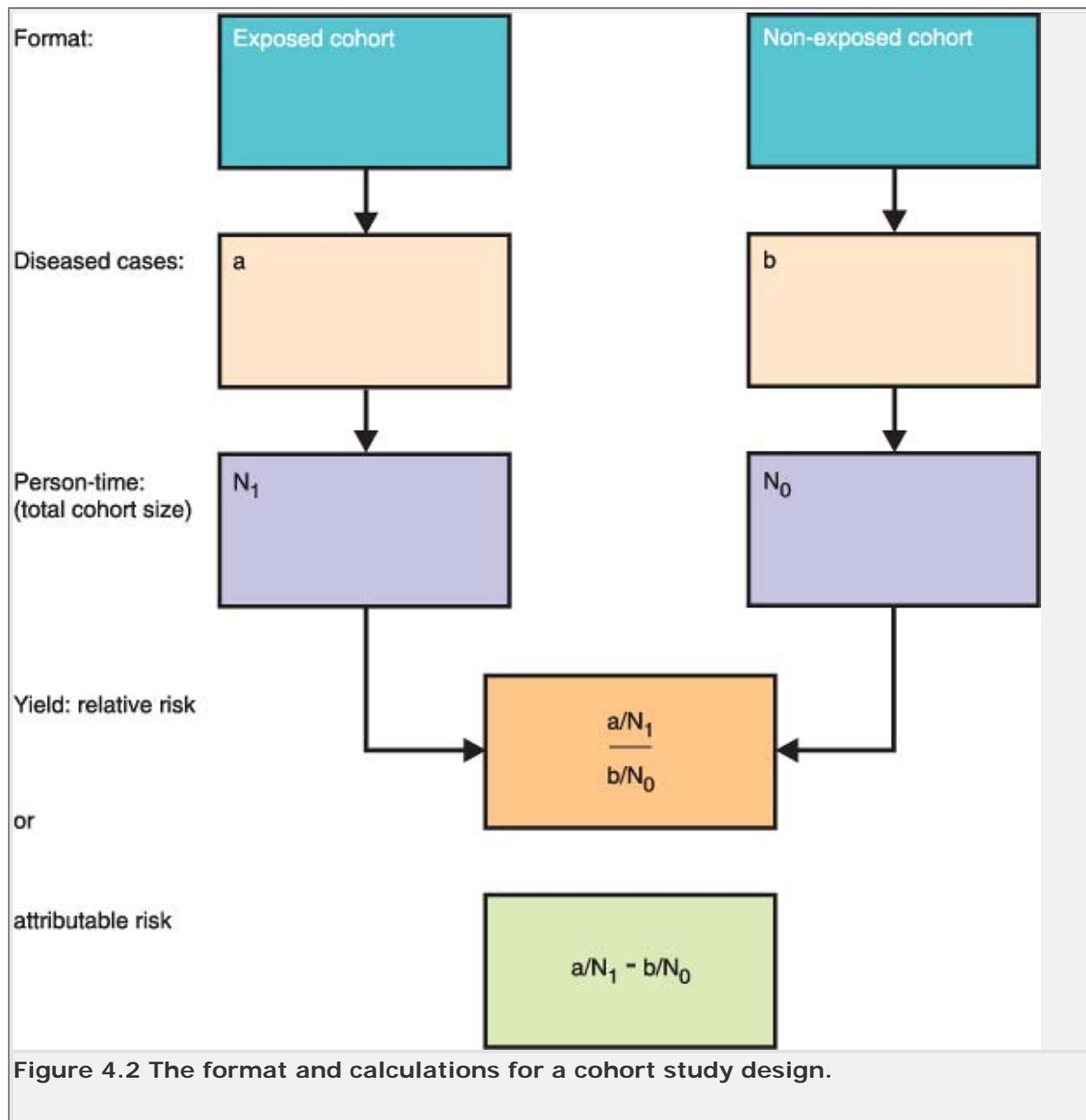
Yield

Cohort studies may yield two measures of an association between exposure and illness. These measures are *attributable risk* and *relative risk*.

- ***Attributable risk* is the difference between the occurrence measure in the exposed and the unexposed cohort.** The null value is zero, indicating no association between exposure and disease; a positive number indicates how many cases

of disease may be caused by the exposure; and a negative number indicates how many cases of disease may be prevented by the exposure.

- ***Relative risk* divides occurrence in the exposed cohort by occurrence in the nonexposed cohort.** The null value for the relative risk is 1. A value greater than 1 indicates that exposure may increase risk for the disease (i.e., a relative risk of 1.5 indicates that exposed individuals had 1.5 times, or 50% greater, the risk for disease as unexposed individuals). A value less than 1 indicates that exposure may decrease risk for disease (i.e., a relative risk of 0.5 indicates that the rate in exposed individuals was half that of the rate in the nonexposed individuals).

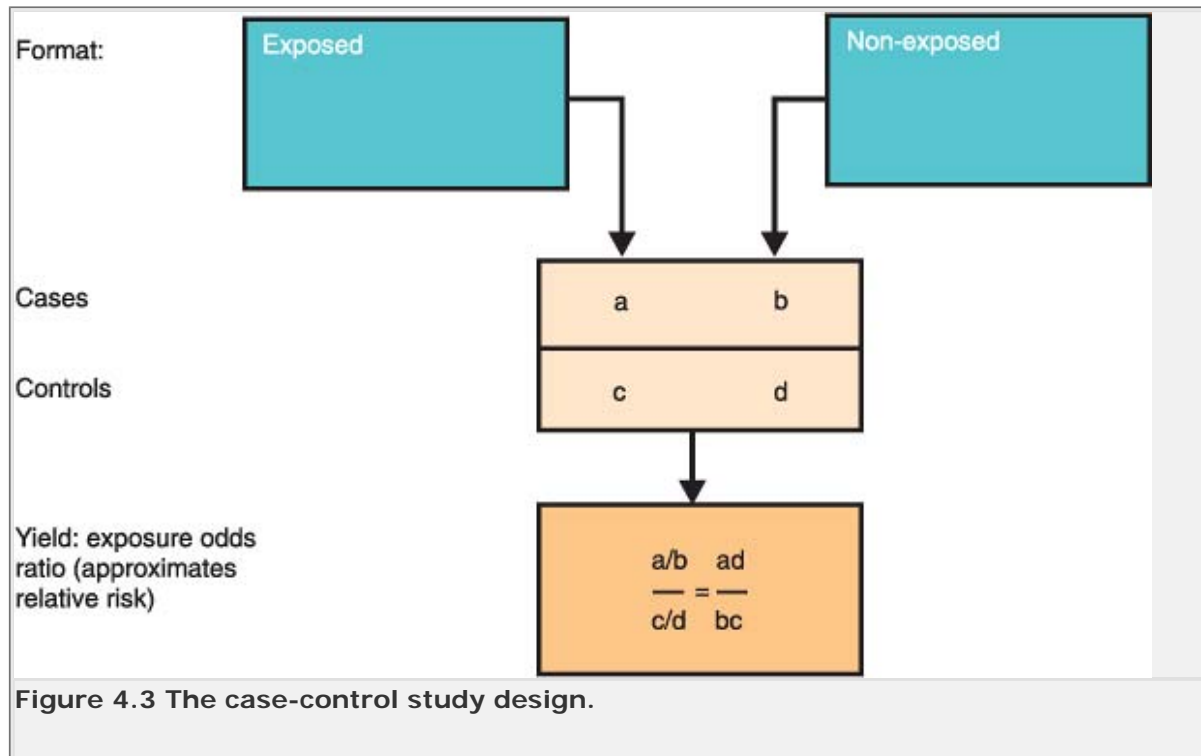


Strengths and Weaknesses

The ability to obtain both attributable and relative risks is a strength of cohort studies. In addition, cohort studies are less susceptible to selection and recall bias.

Misclassification of exposure and confounding variables can occur, however. Disadvantages of a cohort study generally include higher cost and longer time for completion. Cohort studies are most useful for examining the occurrence of common diseases after a rare exposure. For

rare exposures, an investigator may use the general population as the unexposed group. In this type of study, **the observed number of cases in the exposed cohort is divided by the number of cases expected if general population rates had prevailed in the exposed cohort. This comparison is called the *standardized morbidity or mortality ratio (SMR)* and is equivalent to relative risk.**



Case-Control Studies

Design

A case-control study starts with the identification of individuals with a disease or outcome of interest and a suitable control population without the disease or outcome of interest. The controls must be a representative sample of the population from which the cases arose. The relationship of a particular attribute or exposure to the disease is studied by comparing how the cases and controls differed in that exposure. Because the history of exposure before disease is assessed after the disease has occurred, case-control studies are often described as *retrospective*.

Yield

The yield of a case-control study is the exposure odds ratio (or simply *odds ratio*). It is the ratio of exposed cases to unexposed cases divided by the ratio of exposed to unexposed controls (Fig. 4.3). If an entire population could be characterized by its exposure and disease status, the exposure odds ratio would be identical to the relative risk obtainable from a cohort study of the same population. Although it is not feasible to survey the entire population, as long as the sampling of cases or controls from the population was not influenced by their exposure status, the exposure odds ratio will approximate the relative risk. Attributable risk is not directly obtainable in a case-control study. Thus, case-control studies provide only relative measures of risk; they do not give us information about the absolute impact of the exposure.

Strengths and Weaknesses

The advantages of case-control studies are that they are generally lower in cost and easier to conduct than other analytic studies. Case-control studies are most feasible for examining the association between a relatively common exposure and a relatively rare disease. Disadvantages include greater potential for selection bias, information bias, and confounding variables.

Experimental Studies

Because an investigator must assign exposures according to a strict protocol, human experimental studies are limited to the study of measures that will prevent disease or the consequences of disease. Examples of experimental studies are clinical trials and field and community intervention trials.

To improve the availability of information from clinical trials of treatment for serious or life-threatening diseases and conditions, federal law now requires that pharmaceutical companies make this information accessible to patients and members of the public (12).

As a result of this legislation, the Clinical Trials Data Bank became available to the public in February 2000 on the Internet at <http://clinicaltrials.gov> (13).

Clinical Trials

The clinical trial is a prospective cohort study to evaluate treatments for disease in humans. Randomization of the treatment assignment is the cornerstone of a

variables or preferential assignment of treatment based on patient

characteristics. Evidence must be provided that factors that might influence outcome, such as stage of disease, were similar in patients assigned to the study protocol compared with patients assigned to placebo or traditional treatment. A published report of a clinical trial should include a table showing a comparison of the treatment groups with respect to potential confounders to demonstrate the groups did not differ in any important ways before the experimental intervention. Criteria for successful treatment must be clearly defined. Blinding the subject and clinician to the treatment modality may help ensure unbiased assessment of the outcome. A properly designed clinical trial will have a sufficient number of subjects enrolled to ensure that a "negative" study is powerful enough to rule out a treatment effect.

Yield

Clinical trials provide information about both relative and absolute risks. In addition to considering statistical significance, the reader must assess the size of the effect and whether it has clinical significance. Confidence intervals provide information about both the size and significance, and thus provide more information than *p* values alone. **An additional consideration when interpreting study results is that absolute changes in risk are more relevant to patient care than relative changes in risk. The number needed to treat (NNT), provides a measure of the absolute risk. It is the average number of patients that a doctor would need to treat to have one additional event occur.**

Field and Community Intervention Trials

Field and community intervention trials evaluate population measures that may prevent disease, such as vaccines, dietary interventions, or screening procedures. In a field trial, the intervention is applied to individuals. In a community intervention trial, the intervention (e.g., water fluoridation) is applied on a communitywide basis rather than to individuals. Both types of studies include subjects who do not yet have disease and may require large numbers of participants, especially for studies of screening procedures to prevent cancer. In the latter context, issues related to the validity of screening tests (i.e., *sensitivity, specificity, and predictive value*) are quite important (Table 4.2).

Understanding the Results of Analytic Studies

To judge the scientific validity of the results of an analytic study, one needs to consider other possible explanations for the reported association, including **chance, bias** (a systematic error in the way the study was conducted), and **confounding**.

Chance

Statistical inference is the application of statistical methods to quantify how likely it is that the study result is due to chance and to give the reader some idea of the range in which the "true" statistical measure calculated (e.g., mean, proportion, and relative risk) is expected to occur.

Statistical significance is determined by application of a statistical method to test the null hypothesis (i.e., the hypothesis that two or more factors are not associated). The degree of conflict between the test result and the result predicted by the null hypothesis is indicated by the *p value*. Typically, $p \leq 0.05$ is used to determine statistical significance and indicates a 5% chance of incorrectly rejecting the null hypothesis.

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The **confidence interval (CI)** is a component of statistical inference in which an interval is provided to give the reader some idea of the range in which the true statistical measure (e.g., mean, proportion, and relative risk) is expected to occur. A 95% CI implies that if a study were to be repeated many times within the same population, the measures assessed would be expected to fall in this interval 95% of the time. Confidence intervals of 95% for an odds ratio or relative risk that includes the null value of 1 would not be statistically significant.

Table 4.2 Measures of Validity for a Screening Procedure			
<i>True Disease Status</i>			
<i>Status Determined by Screening</i>	<i>Positive</i>	<i>Negative</i>	<i>Total</i>
Positive	a (true positives)	b (false-positives)	a + b (all screened positives)
Negative	c (false-negatives)	d (true negatives)	c + d (all screened negatives)
Total	a + c (all diseased)	b + d (all nondiseased)	N (all subjects)
<i>Measure</i>	<i>Definition</i>	<i>Formula</i>	
Sensitivity	$\frac{\text{True positives}}{\text{All diseased}}$	$\frac{a}{a + c}$	
Specificity	$\frac{\text{True negatives}}{\text{All nondiseased}}$	$\frac{d}{b + d}$	
Predictive value of a positive screen	$\frac{\text{True positives}}{\text{All screened positives}}$	$\frac{a}{a + b}$	

From **Cramer DW**. Epidemiology and biostatistics. In: **Berek JS, Hacker NF**, eds. *Gynecologic oncology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005:258, with permission.

Table 4.2 Measures of Validity for a Screening Procedure

Bias

Bias is a systematic error in the design, conduct, or analysis of a study. Such errors result in a mistaken conclusion and can take various forms. It is important for the investigator to anticipate the types of bias that might occur in a study and correct them during the design of the study, because it may be difficult or impossible to correct for them in the analysis.

- **Information bias occurs when subjects are classified incorrectly with respect to exposure or disease.** This may occur if records are incomplete or if the criteria for exposure or outcome were poorly defined, leading to misclassification.
- **Recall bias is a specific type of information bias that may occur if cases are more likely than controls to remember or to reveal past exposures.** For example, in a study of antenatal medication exposure and birth defects, a mother with an infant born with a birth defect may be more likely to report exposures than a woman with a healthy infant. In addition to adequate criteria and complete records, information bias may be reduced by making interviewers unaware of the status of the subjects or the purpose of the study whenever possible.
- **Selection bias may occur when correlates of the exposure or outcome influence sampling from the larger population of potentially eligible subjects.** An example of selection bias that may arise in a hospital-based case-control study occurs when the combination of the disease under study and a particular exposure is more likely to lead to hospital admission (14). Using incident cases from more than one hospital, obtaining high participation rates, and attempting to describe nonparticipants

are several ways to reduce or at least evaluate the potential for selection bias.

Confounding

- **A confounder is an extraneous variable that accounts for the apparent effect of the study variable or masks the true association.**
- **When a factor differs between cases and controls or cohort members and is**

associated with both the study exposure and the study outcome, a distortion of the true association between the exposure and the disease may be produced.

Age, race, and socioeconomic status are likely confounders; results must be adjusted for these variables by using statistical techniques such as stratification or multivariate analysis. Stratification involves examining the association of interest only within groups that are similar with respect to a potential confounder. Multivariate analysis is a statistical technique commonly used in epidemiologic studies that controls a number of confounders simultaneously. After an analysis to control for confounding variables, the investigator presents the adjusted odds ratio or relative risk that presumably reflects an association free of confounding.

Assessing Causality

In addition to an unbiased design, there are a number of factors that, when present, strengthen the likelihood that the factors being studied are causally related rather than just associated.

- ***Dose response*** means that a change in the amount, intensity, or duration of an exposure is associated with either a consistent increase or decrease in risk for a specified disease or outcome. Trend tests are used to determine whether a dose response exists.
- ***Consistency*** between findings in different populations, at different times, and by different methods or investigators is an important criterion used to judge whether there is likely to be a causal relationship. A formal method for studying consistency and pooling results from different studies is meta-analysis. ***Meta-analysis*** is the process of combining results from several independent studies examining the same exposure (or treatment) and same outcome to conduct a more powerful test of the null hypothesis. A meta-analysis is conducted by assembling measures of the association from different studies, such as relative risks, weighting them by the variance of the measure, and taking an overall average. In the weighting process, the studies with the largest sample size contribute the greatest information. A properly performed meta-analysis also has a qualitative component that establishes criteria for acceptance of a study (e.g., only randomized studies might be chosen for a meta-analysis of the effect of a particular treatment on a particular disease).
- ***Biologic credibility*** means that an association is plausible, taking into consideration all aspects of what is known about the natural history or demographics of a disease or what has been observed in relevant experimental models. Whereas an

imaginative epidemiologist can find an explanation for any single association, a key issue is whether a model can be proposed accounting for a variety of exposures as well as experimental data and cross-sectional observations.

Reproductive Epidemiology

Although there is no standard definition of what constitutes "reproductive epidemiology," theoretically it could include the domain of epidemiologic studies addressing reproductive (or gynecologic) events that affect common diseases in women and common exposures that affect reproductive or gynecologic diseases.

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Reproductive Events

Age at menarche, characteristics of menstrual cycles, number of pregnancies, contraceptives or hormones used, and age at menopause are important events that may have broad impact on many diseases, including endometriosis (15), fibroids (16), heart disease (17), osteoporosis (18), and cancers of the breast, endometrium, or ovary (19,20,21). Gynecologists should maintain careful records of reproductive landmarks, both for their potential usefulness in advising patients and for their relevance to clinical research.

Contraception and Sterilization

Barrier Contraception

Barrier contraception includes spermicides, vaginal barriers (cervical caps, diaphragms, and female condoms), and male condoms. In general, a protective effect of barrier contraception against pelvic inflammatory disease (PID) (22), tubal infertility (23), ectopic pregnancy (24), and cervical cancer (25) has been consistently observed. However, **spermicides appear not to protect against HIV transmission (26), and use of synthetic condoms is recommended. Women using the diaphragm are at an increased risk of symptomatic urinary tract infection (27).**

Intrauterine Devices

Current or past use of an intrauterine device has been linked with risk for PID (28), ectopic pregnancy (29), and tubal infertility (30). It is likely that these risks could

be reduced by restricting IUD use to women at low risk for genital infections (e.g., women in mutually monogamous relationships). In addition to providing effective long-term contraception, the IUD has been shown to have noncontraceptive benefits. A recent comprehensive review of the association between copper-bearing IUDs and risk of and endometrial cancer provides good evidence for this protective effect, with the risk in IUD users reduced by approximately 50% (31). There is some evidence that IUD use may also reduce the risk for ovarian cancer, perhaps through an immune-mediated mechanism that might also pertain to the association with endometrial cancer. Levonorgestrel-containing IUDs have been shown to be effective for the treatment of idiopathic menorrhagia (32).

Oral Contraceptives

Early epidemiologic research on oral contraceptives (OCs) focused on adverse events, including thromboembolism (particularly with high-dose formulations) (33), hypertension (34), myocardial infarction (especially in women older than 40 years of age who also smoked) (35), and liver adenomas (36). **Protective effects of OCs have more recently been appreciated, including lower risk for benign breast disease (37), ovarian cysts (38), ovarian cancer (39), and PID (40).** Controversy exists concerning the relationship between OC use and cervical and breast cancer. The results of a large observational study suggested that women who were currently taking oral contraceptives and as well as those who had stopped within 10 years had a small but significant increase in the risk of breast cancer that declined with time since last use (41). The possible increased risk of developing breast cancer at an early age associated with past OC use may be more than offset by a decreased risk for developing breast cancer at an older age (42). There is a modest but fairly consistent association between OC use and cervical cancer (43) that may relate to an interaction with human papillomavirus (HPV) infection (44).

Long-Acting Progestin Contraceptives

Long-term use of depot medroxyprogesterone acetate (DMPA), a progestin hormonal contraceptive, can result in significant bone loss, which may not be entirely reversible (45,46). Although FDA labeling recommends the use of DMPA for more than 2 years only

under circumstances when other methods are inadequate (47); the World Health Organization Statement on Hormonal Contraception and Bone Health recommends no restriction on duration of use among women aged 18–45 years old, given the insufficient data on DMPA use and risk of fracture in menopause (48).

Sterilization

Concerns that sterilization might induce early menopause (49) have not been proved.

An unexpected effect of female sterilization may be protection from ovarian cancer (50).

This protection may derive from interruption of the utero-ovarian circulation or from closure of the female tract, which would prevent substances in the vagina or uterus from reaching the ovaries. Alternatively, it has been speculated that tubal ligation may predispose women to the formation of antibodies that protect against the development of ovarian cancer (51).

Hormone Replacement Therapy

Early studies of menopausal hormones identified increased risk of endometrial cancer associated with unopposed estrogen use (52). This association has likely been obviated by the use of combined estrogen–progesterone regimens (53). Although observational studies suggested protective effects on heart disease (54), osteoporosis (55), and even Alzheimer's disease (56), recent clinical trials have questioned some of these benefits. **The Heart and Estrogen/progestin Replacement Study (HERS), a randomized controlled trial of hormone therapy (HT) in more than 2,700 women with documented coronary heart disease, found no benefit of HT for secondary prevention of coronary heart disease (CHD) (57,58). The Women's Health Initiative (WHI) is a national study that included a randomized controlled trial of HT for prevention of disease in postmenopausal women. In the combined estrogen–progestin portion of the study, which included approximately 16,000 women without preexisting CHD, a 29% increased risk of primary CHD events (95% CI 1.02–1.63) was found (59). Although benefits were seen for the prevention of colon cancer (Hazard Ratio [HR] = 0.63; 95% CI 0.43–0.92) and hip fracture (HR = 0.66; 95% CI 0.45–0.98), the risk of breast cancer was increased (HR = 1.26; 95% CI 1.00–1.59) and total mortality in the HT group was higher (HR = 1.15; 95% CI 1.05–1.28). Thus, HT is recommended only for the treatment of menopausal symptoms, not for the primary prevention of other diseases (60) (see Chapter 32).**

The reason for the discrepancy between the randomized controlled trials of estrogen for primary and secondary disease prevention and the observational studies has been the subject of discussion among epidemiologists (61). Selection bias due to the health-user effect has been suggested as the reason for this difference (62). However, a biologically plausible reason for this discrepancy is that the populations studied were substantially different; in observational studies, most women started HT at the time of menopause, whereas many women in randomized studies started HT remote from the time of menopause (63).

The association between menopausal hormones and breast cancer also continues to be debated. A recent meta-analysis of studies of menopausal hormone use and breast cancer provided reassurance that the effect of such agents on breast cancer risk is modest (64). **In**

the WHI, women taking combined estrogen and progestin HT had an increased risk of breast cancer compared with placebo (HR = 1.26; 95% CI 1.00-1.59); however, no increased risk was seen in the estrogen alone HT component of the study (HR = 0.77; 95% CI 0.59-1.01) (65) (see Chapter 32). Thus, progestin use is likely to play an important role in whether an HT regimen increases the risk of breast cancer.

Sexually Transmitted Disease

Worldwide, sexually transmitted diseases are possibly the most important preventable cause of morbidity in women. This morbidity includes not only PID from gonorrhea and chlamydia but also chronic disease from syphilis and genitally transmitted viruses, including hepatitis, HPV, and HIV. Based on epidemiologic data, the most consistent risk factor for chlamydia infection is age; thus the Centers for Disease Control and Prevention recommends

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annual screening for all sexually active women younger than the age of 25 (66). Epidemiologic data have also been used to recommend strategies for the evaluation of Pap test results showing atypical cells of undetermined significance (ASCUS) based on the presence of high-risk HPV subtypes (67). The importance of public health measures to prevent the spread of sexually transmitted diseases, especially the use of barrier contraception, cannot be overemphasized; the morbidity from these infections may carry over to the offspring of those infected.

Lifestyle

An appreciation of lifestyle factors that increase or decrease risk for disease allows the physician to suggest important changes in behavior that can prevent disease and improve patients' health. Assessment and evaluation of some of the following factors should be a part of the annual history and physical examination.

Smoking, Alcohol, and Caffeine

About 20% of women in the United States smoke tobacco, consume two or more cups of coffee per day, or have four or more alcoholic drinks per week. As a result, these behaviors are significant to reproductive epidemiology. Adverse effects of smoking on the lungs and heart are well known; however, it is less widely appreciated that smoking may be linked to tubal infertility (68), ectopic pregnancy (69), cervical cancer (70), and early menopause (71). In moderation, alcohol use is associated with decreased risk of cardiovascular disease (72), which is offset by an increased risk for breast cancer (73). Alcohol use also has been associated with an increased risk of endometriosis and fibroids (74,75). It

is possible that these effects are mediated by the ability of alcohol to retard the metabolism of estrogen, thereby leading to higher circulating levels of estrogen (76). Alternatively, some investigators have attributed the adverse effects of alcohol to folate deficiency and suggested that they could be countered with folate supplementation (77). Coffee consumption is the major source of caffeine in the diet and is another very common exposure that has been extensively investigated with regard to gynecologic problems. The effects of caffeine on delayed conception and spontaneous abortion have been of particular interest. In one study, women consuming more than five cups of coffee per day (equivalent to more than 500 mg of caffeine) were 1.45 times more likely to need more than 9 months to conceive compared with women who did not regularly consume caffeine (78). Regarding spontaneous abortion, a high-profile article suggested that caffeine intake above the level of 500 mg may increase the risk for abortion of a karyotypically normal fetus (79), whereas another review concluded that the evidence was equivocal given potential biases related to recall and selection as well as confounding variables (80).

Exercise and Nutrition

Exercise and nutrition have broad implications to women's health, and gynecologic problems can occur at either extreme. The lean athlete in training who becomes amenorrheic may lose bone mass because of a lack of estrogen, as might the patient with anorexia (23). In obese women, menstrual difficulties may occur that are related to higher estrogen levels, which may, in the longer term, be associated with a higher risk for endometrial cancer (81) and postmenopausal breast cancer (82). Indeed, there is almost no aspect of gynecologic or obstetric care that is not affected by obesity (83).

Talc

Use of talc in genital hygiene is an exposure emphasized as a potential risk factor for ovarian cancer (84). Because genital talc use has no benefit other than aesthetic purposes, this practice should be discouraged.

Illnesses and Mortality Statistics

Many gynecologists are primary care providers for women, and they may increasingly assume this role in the future. It is important, therefore, for gynecologists to be aware of the major causes of mortality in women.

Table 4.3 shows the 10 leading causes of death in 2002 for women in the United States by age from the National Center for Health Statistics data (85). **Heart disease remains the major**

cause of death in women overall, but there is considerable age variation. Accidents and homicides, and suicides are most important at ages younger than 40 years, and cancer is most important at ages 40 to 79 years.

Table 4.3 Reported Deaths for the 10 Leading Causes of Death by Age, United States, 2002						
	All Ages	1-19 Yr	20-39 Yr	40-59 Yr	60-79 Yr	80+Yr
	<i>All causes: 983,940</i>	<i>All causes: 6,993</i>	<i>All causes: 22,204</i>	<i>All causes: 104,055</i>	<i>All causes: 336,929</i>	<i>All causes: 523,794</i>
1	Heart diseases: 356,014	Accidents: 3,778	Accidents: 6,859	Cancer: 49,570	Cancer: 129,699	Heart diseases: 231,969
2	Cancer: 268,503	Cancer: 957	Cancer: 5,403	Heart diseases: 21,677	Heart diseases: 99,160	Cancer: 82,840
3	Cerebrovascular diseases: 100,050	Homicide: 636	Heart diseases: 2,640	Accidents: 8,076	Chronic obstructive pulmonary diseases: 29,905	Cerebrovascular diseases: 67,702
4	Chronic obstructive pulmonary diseases: 64,103	Congenital anomalies: 552	Suicide: 1,913	Cerebrovascular diseases 5,536	Cerebrovascular diseases 25,934	Alzheimer's diseases 35,225
5	Alzheimer's disease: 41,877	Heart diseases: 332	Homicide: 1,723	Diabetes mellitus: 4,675	Diabetes mellitus: 17,038	Chronic obstructive pulmonary diseases: 29,619
6	Diabetes mellitus: 38,948	Suicide: 298	HIV: 1,391	Chronic obstructive pulmonary diseases: 4,089	Pneumonia and influenza: 7,508	Pneumonia and influenza: 27,094
7	Accidents: 37,485	Pneumonia and influenza: 134	Cerebrovascular diseases: 740	Liver diseases: 3,617	Nephritis: 7,375	Diabetes mellitus: 16,566
8	Pneumonia and influenza 36,763	Chronic obstructive pulmonary diseases: 108	Diabetes: mellitus: 629	Suicide: 2,879	Accidents: 6,987	Nephritis: 11,784
9	Nephritis: 21,279	Septicemia: 108	Liver disease: 475	HIV: 1,998	Septicemia: 6,781	Accidents: 11,381
10	Septicemia: 18,918	Benign neoplasms: 90	Congenital anomalies: 431	Septicemia: 1,938	Alzheimer's disease: 6,542	Septicemia: 9,614

HIV, human immunodeficiency virus.

From **National Center for Injury Prevention and Control, Centers for Disease Control and Prevention**. Web-based Injury Statistics Query and Reporting System (WISQARS) [online] (2004). Centers for Disease Control and Prevention. Available at: <http://www.cdc.gov/ncipc/wisqars>. Accessed April 25, 2005.

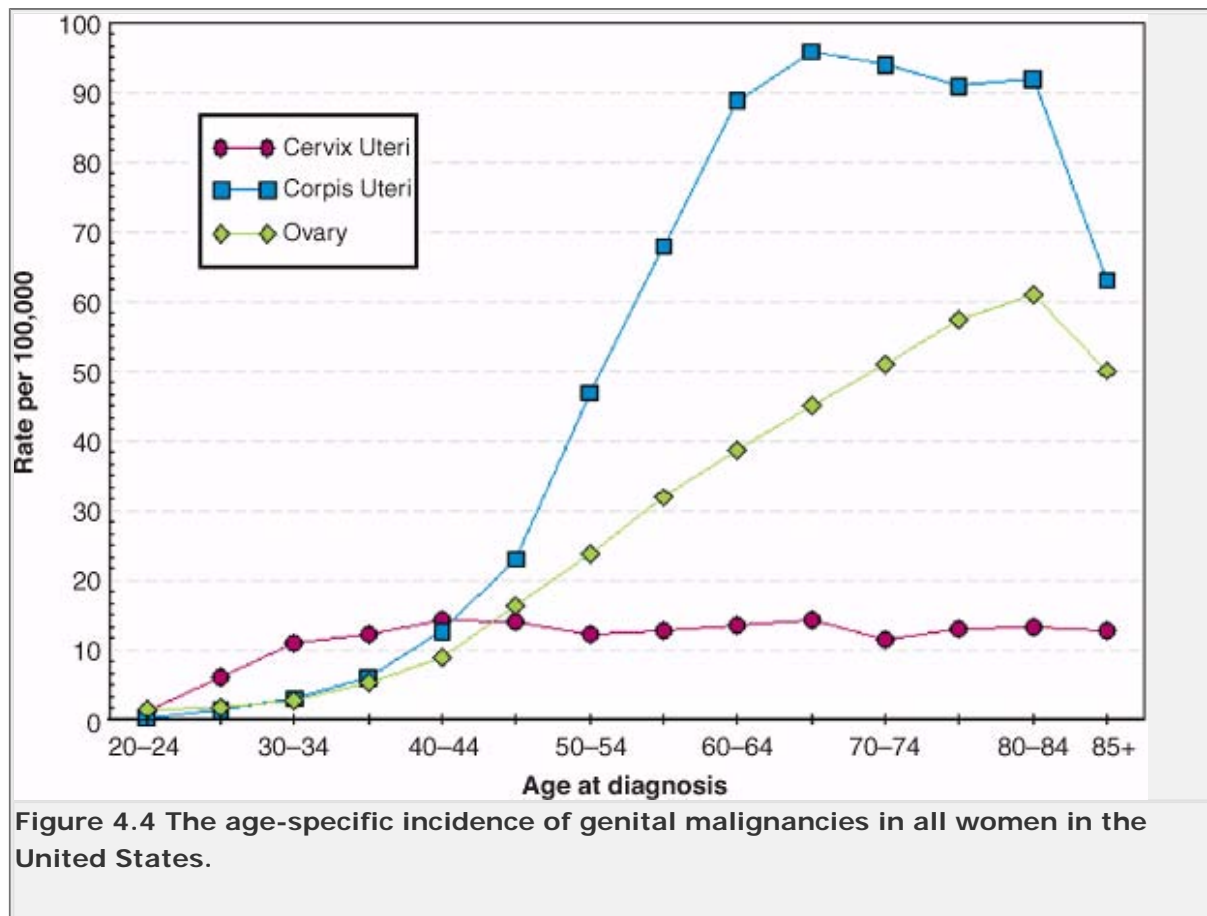
Table 4.4 Age Distribution of Incidence Cancer Cases by Site in Females, 1997–2001

	<i>All Ages</i>	<i>20–34</i>	<i>35–44</i>	<i>45–54</i>	<i>55–64</i>	<i>65–74</i>	<i>75–84</i>	<i>85 +</i>
Breast (females)	208,089	2,497	14,358	31,838	37,040	45,572	47,444	29,132
Cervix	21,335	1,281	3,652	4,736	3,712	3,414	2,944	1,600
Corpus and uterus, NOS	32,445	162	649	2,336	5,191	9,052	9,863	5,191
Ovary	68,998	552	2,415	7,659	12,075	18,422	19,664	8,211

NOS, not otherwise specified.

From **Ries LAG, Eisner MP, Kosary CL, et al.** (eds). SEER Cancer Statistics Review, 1975–2002, National Cancer Institute, Bethesda, MD, based on November 2004 SEER data submission, posted to the SEER Web site 2005. Available at: http://seer.cancer.gov/csr/1975_2002. Accessed April 25, 2005.

Table 4.4 shows the incidence of gynecologic cancers over a 5-year period from 1997 to 2001 by various ages (86). Figure 4.4 illustrates the age-specific incidence of genital malignancies in all women in the United States (87). **The incidence of invasive cervical cancer remains fairly steady across all ages, whereas ovarian and endometrial cancer increase markedly during the perimenopausal years and predominate after 50 years of age.** The sharp increase in endometrial and ovarian cancer rates around the time of menopause may reflect anovulatory cycles associated with unopposed estrogen and increased levels of gonadotropins. Although ovarian cancer appears to rank second to endometrial cancer in terms of incidence, mortality from ovarian cancer currently exceeds the combined mortality of endometrial and cervical cancer (88).



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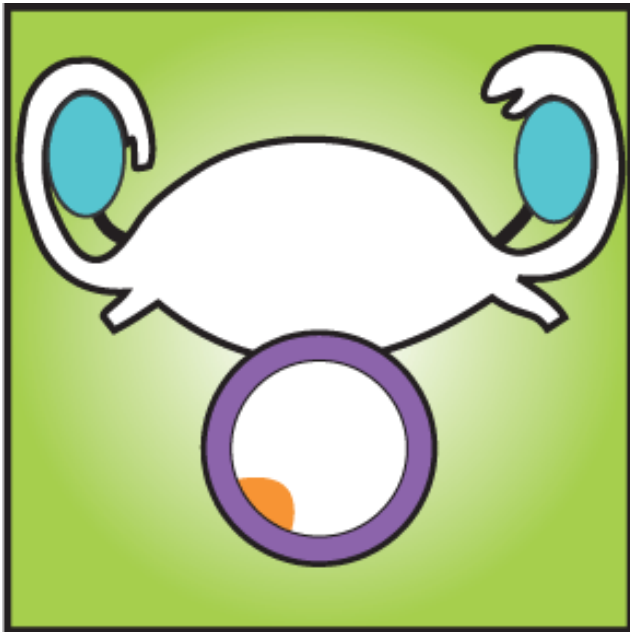
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5

Anatomy and Embryology

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- **Although the basic facts of anatomy do not change, our understanding of specific anatomic relationships and the development of new clinical and surgical correlations continue to evolve.**

- **There is significant variation in the branching pattern of pelvic blood vessels between individuals, and patterns of blood flow may be asymmetric from side to side in the same individual. The pelvic surgeon should be prepared for deviations from "textbook" vascular patterns.**
- **An understanding of the development of pelvic floor disorders and their safe and effective management requires a comprehensive understanding of the interrelationships between the bony pelvis and its ligaments, pelvic muscles and fasciae, nerves and blood vessels, and pelvic viscera.**
- **About 10% of infants are born with some abnormality of the genitourinary system, and anomalies in one system are often mirrored by anomalies in another system with special implications in pelvic surgery.**
- **About 75% of all iatrogenic injuries to the ureter result from gynecologic procedures, most commonly abdominal hysterectomy; risk is increased with distortions of pelvic anatomy, including adnexal masses, endometriosis, other pelvic adhesive disease, or fibroids.**

An understanding of the anatomy of the female pelvis is fundamental to the knowledge base of a practicing gynecologist. Although the basic facts of anatomy and their relevance to gynecologic practice do not change with time, our understanding of specific anatomic relationships and the development of new clinical and surgical correlations continue to evolve.

The anatomy of the fundamental supporting structures of the pelvis and the genital, urinary, and gastrointestinal viscera are presented in this chapter. Because significant variation has developed in the names of many common anatomic structures, the terms used here reflect

current standard nomenclature according to the *Nomina Anatomica* (1); however, other commonly accepted terms are included in parentheses.

Pelvic Structure

Bony Pelvis

The skeleton of the pelvis is formed by the sacrum and coccyx and the paired hip bones (coxal, innominate), which fuse anteriorly to form the symphysis pubis. Figure 5.1 illustrates the bony pelvis as well as its ligaments and foramina.

Sacrum and Coccyx

The sacrum and coccyx are an extension of the vertebral column resulting from the five fused sacral vertebrae and the four fused coccygeal vertebrae. They are joined by a symphyseal articulation (sacrococcygeal joint), which allows some movement.

The essential features of the sacrum and coccyx are as follows:

- **Sacral promontory**—the most prominent and anterior projection of the sacrum, this is an important landmark for insertion of a laparoscope. It is located at the level of bifurcation of the common iliac arteries.
 - **Four paired anterior and posterior sacral foramina**—exit sites for the anterior and posterior rami of the corresponding sacral nerves; anterior foramina are also traversed by the lateral sacral vessels.
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- **Sacral hiatus**— results from incomplete fusion of the posterior lamina of the fifth sacral vertebra, offering access to the sacral canal, which is clinically important for caudal anesthesia.

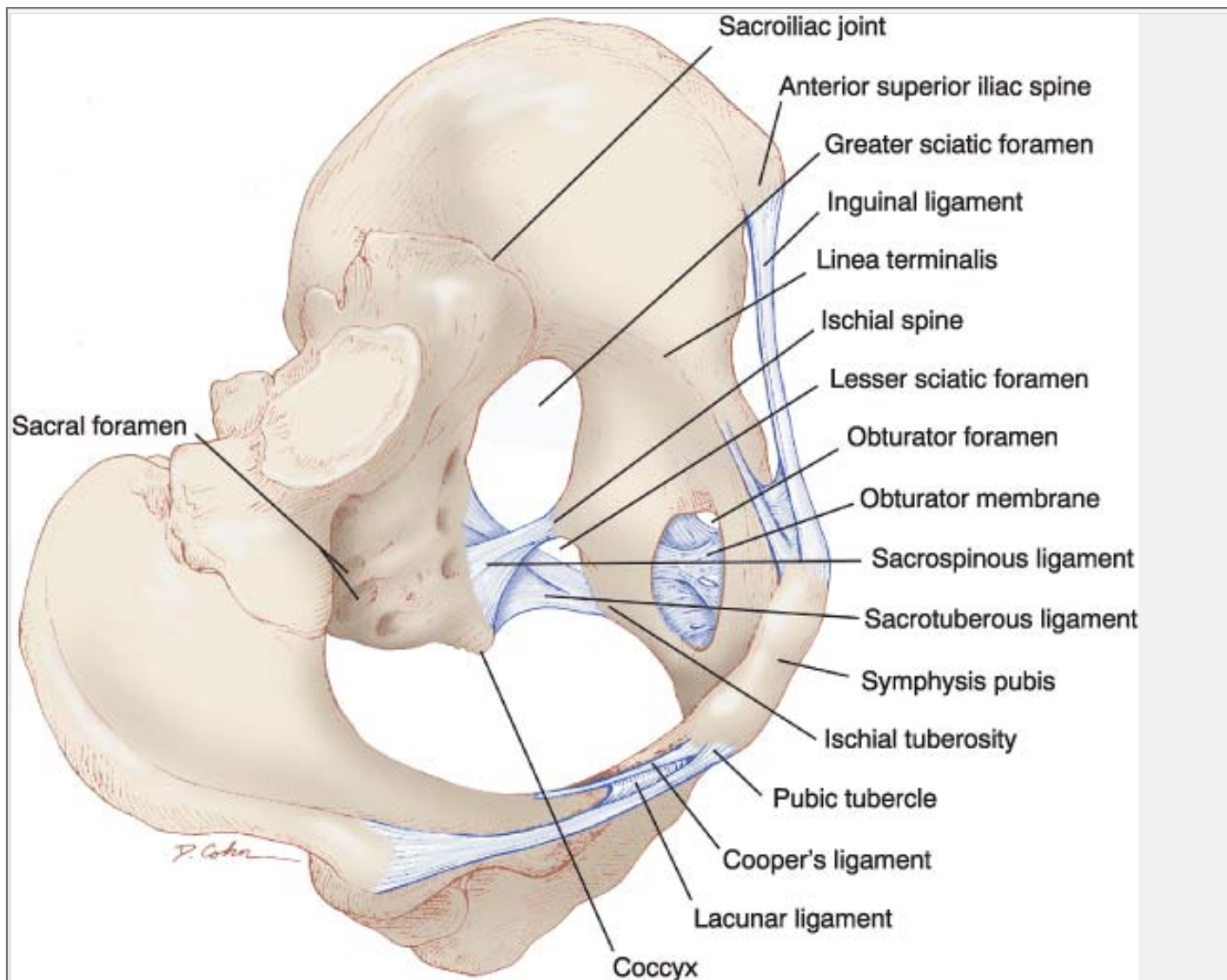


Figure 5.1 The female pelvis. The pelvic bones (the innominate bone, sacrum, and coccyx) and their joints, ligaments, and foramina.

Laterally, the alae (“wings”) of the sacrum offer auricular surfaces that articulate with the hipbones to form synovial sacroiliac joints.

Os Coxae

The paired *os coxae*, or hip bones, have three components: the ilium, the ischium, and the

pubis. These components meet to form the acetabulum, a cup-shaped cavity that accommodates the femoral head.

Ilium

- **Iliac crest**—provides attachments to the iliac fascia, abdominal muscles, and fascia lata.
- **Anterior superior and inferior spine**—superior spine provides the point of fixation of the inguinal ligament.
- **Posterior superior and inferior spine**—superior spine is the point of attachment for the sacrotuberous ligament and the posterior sacral iliac ligament.
- **Arcuate line**—marks the pelvic brim and lies between the first two segments of the sacrum.
- **Iliopectineal eminence (linea terminalis)**—the line of junction of the ilium and the pubis.
- **Iliac fossa**—the smooth anterior concavity of the ilium, covered by the iliacus muscle.

Ischium

- **Ischial spine**—delineates the greater and lesser sciatic notch above and below it. It is the point of fixation for the sacrospinous ligament; the ischial spine represents an important landmark in the performance of pudendal nerve block and sacrospinous ligament vaginal suspension; vaginal palpation during labor allows detection of progressive fetal descent.
- **Ischial ramus**—joins that of the pubic rami to encircle the obturator foramen; provides the attachment for the inferior fascia of the urogenital diaphragm and the perineal

musculofascial attachments.

- **Ischial tuberosity**—the rounded bony prominence upon which the body rests in the sitting position.

Pubis

- **Body**—formed by the midline fusion of the superior and inferior pubic rami.

- **Symphysis pubis**—a fibrocartilaginous symphyseal joint where the bodies of the pubis meet in the midline; allows for some resilience and flexibility, which is critical during parturition.

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- **Superior and inferior pubic rami**—join the ischial rami to encircle the obturator foramen; provide the origin for the muscles of the thigh and leg; provide the attachment for the inferior layer of the urogenital diaphragm.

- **Pubic tubercle**—a lateral projection from the superior pubic ramus, to which the inguinal ligament, rectus abdominis, and pyramidalis attach.

Clinical Considerations

Recent studies using magnetic resonance imaging (MRI) or computed tomography (CT) pelvimetry have found an association between the architecture of the bony pelvis, specifically a wider transverse inlet (distance between the most superior aspects of the iliopectineal line) (2,3) and a shorter obstetric conjugate (shortest distance between the sacral promontory and the pubic symphysis), and the occurrence of pelvic floor disorders (3). It is speculated that women with these characteristics may be more likely to suffer neuromuscular and connective tissue injuries during labor and delivery, predisposing them to the development of pelvic neuropathy or pelvic organ prolapse or both. There may be a potential role for imaging of the

bony pelvis to identify those women most likely to benefit from cesarean delivery for the prevention of pelvic floor disorders.

Pelvic Bone Articulations

The pelvic bones are joined by four articulations:

- **Two cartilaginous symphyseal joints—the sacrococcygeal joint and the symphysis pubis**—these joints are surrounded by strong ligaments anteriorly and posteriorly, which are responsive to the effect of relaxin and facilitate parturition.
- **Two synovial joints—sacroiliac joints**—these joints are stabilized by the sacroiliac ligaments, the iliolumbar ligament, the lateral lumbosacral ligament, the sacrotuberous ligament, and the sacrospinous ligament.

The pelvis is divided into the *greater* and *lesser pelvis* by an oblique plane passing through the sacral promontory, the *linea terminalis (arcuate line of the ilium)*, the *pectineal line of the pubis*, the *pubic crest*, and the *upper margin of the symphysis pubis*. This plane lies at the level of the superior pelvic aperture (*pelvic inlet*) or pelvic brim. The inferior pelvic aperture or *pelvic outlet* is irregularly bound by the tip of the coccyx, the symphysis pubis, and the ischial tuberosities. The dimensions of the superior and inferior pelvic apertures have important obstetric implications.

Ligaments

Four ligaments—inguinal, Cooper's, sacrospinous, and sacrotuberous—of the bony pelvis are of special importance to the gynecologic surgeon.

Inguinal Ligament

The inguinal ligament is important surgically in the repair of inguinal hernia. The inguinal ligament:

-

Is formed by the lower border of the aponeurosis of the external oblique muscle folded back upon itself.

- Is fused laterally to the iliacus fascia and inferiorly to the fascia lata.
- Flattens medially into the lacunar ligament, which forms the medial border of the femoral ring.

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Cooper's Ligament

Cooper's ligament is used frequently in bladder suspension procedures. Cooper's ligament:

- Is a strong ridge of fibrous tissue extending along the pectineal line—also known as the pectineal ligament.
- Merges laterally with the iliopectineal ligament and medially with the lacunar ligament.

Sacrospinous Ligament

The sacrospinous ligament is often used for vaginal suspension. This ligament offers the advantage of a vaginal surgical route. The sacrospinous ligament:

- Extends from the ischial spine to the lateral aspect of the sacrum.
- Is separated from the rectovaginal space by the rectal pillars.
- Lies anterior to the pudendal nerve and the internal pudendal vessels at its attachment to the ischial spine.

The inferior gluteal artery, with extensive collateral circulation, is found between the sacrospinous and sacrotuberous ligaments and may be injured during sacrospinous suspension (4) (Fig. 5.2). Injury to the inferior gluteal artery, as well as to the pudendal nerve and internal pudendal vessels, during sacrospinous ligament suspension may be minimized by

careful and controlled retraction and suture placement at least two fingerbreadths medial to the ischial spine.

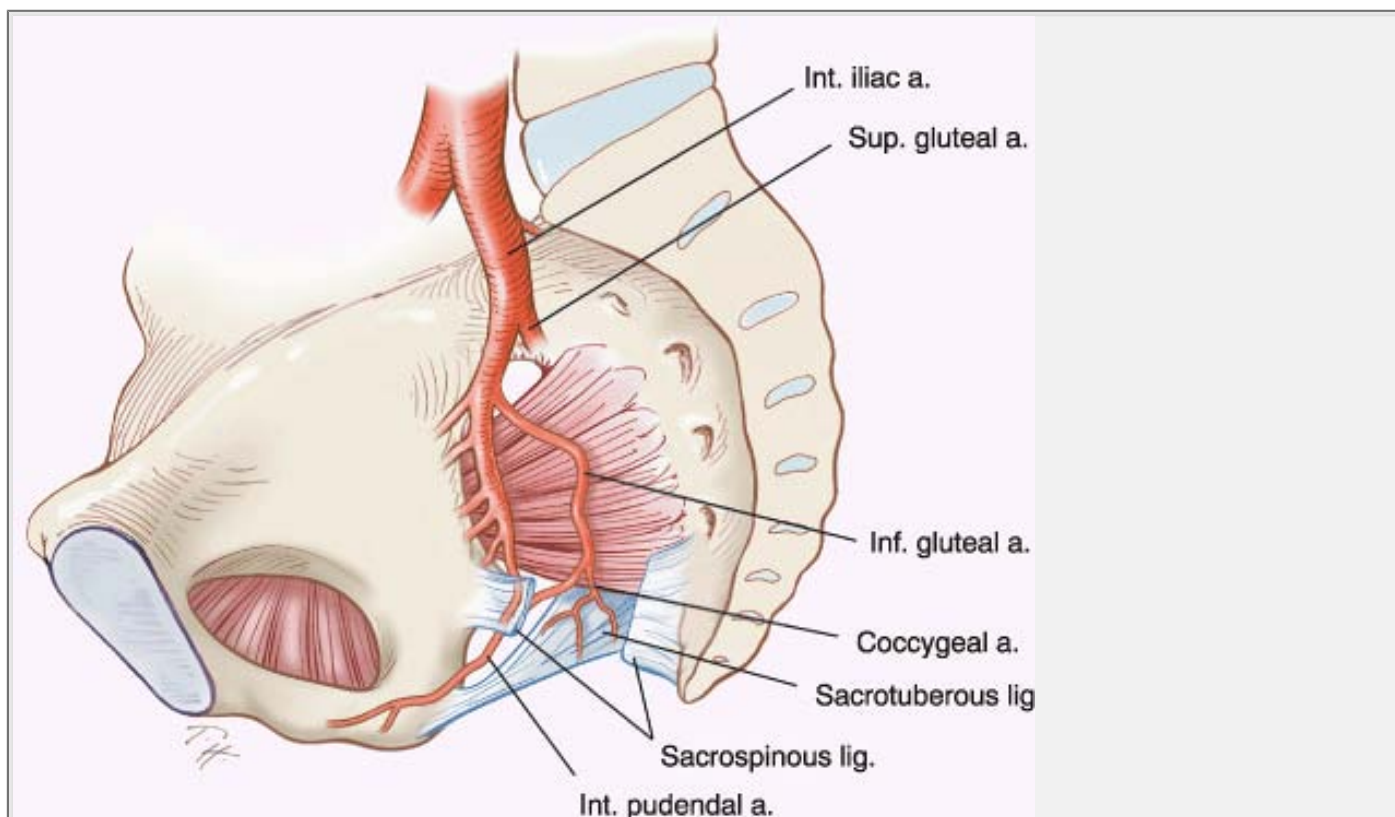


Figure 5.2 Tone drawing of left hemipelvis with sacrospinous ligament reflected. a. = artery; Inf. = inferior; lig. = ligament; n. = nerve; Sacrosp. = sacrospinous; Sacrotub. = sacrotuberous. (Redrawn from **Thompson JR, Gibbs JS, Genadry R, et al.** Anatomy of pelvic arteries adjacent to the sacrospinous ligament: importance of the coccygeal branch of the inferior gluteal artery. *Obstet Gynecol* 1999;94(6):973–977, with permission.)

Sacrotuberous Ligament

The sacrotuberous ligament is sometimes used as a point of fixation for vaginal vault suspension. The sacrotuberous ligament:

- Extends from the ischial tuberosity to the lateral aspect of the sacrum.
- Merges medially with the sacrospinous ligament.
- Lies posterior to the pudendal nerve and the internal pudendal vessels.

Foramina

The bony pelvis and its ligaments delineate three important foramina that allow the passage of the various muscles, nerves, and vessels to the lower extremity.

Greater Sciatic Foramen

The greater sciatic foramen transmits the following structures: the piriformis muscle, the superior gluteal nerves and vessels, the sciatic nerve along with the nerves of the quadratus femoris, the inferior gluteal nerves and vessels, the posterior cutaneous nerve of the thigh, the nerves of the obturator internus, and the internal pudendal nerves and vessels.

Lesser Sciatic Foramen

The lesser sciatic foramen transmits the tendon of the obturator internus to its insertion on the greater trochanter of the femur. The nerve of the obturator internus and the pudendal vessels and nerves reenter the pelvis through it.

Obturator Foramen

The obturator foramen transmits the obturator nerves and vessels. The obturator neurovascular bundle can be potentially injured during transobturator tape placement, a procedure for treatment of urinary incontinence. Injury can be prevented by careful identification of anatomic landmarks and placement away from the obturator foramen.

Muscles

The muscles of the pelvis include those of the lateral wall and those of the pelvic floor (Fig. 5.3; Table 5.1).

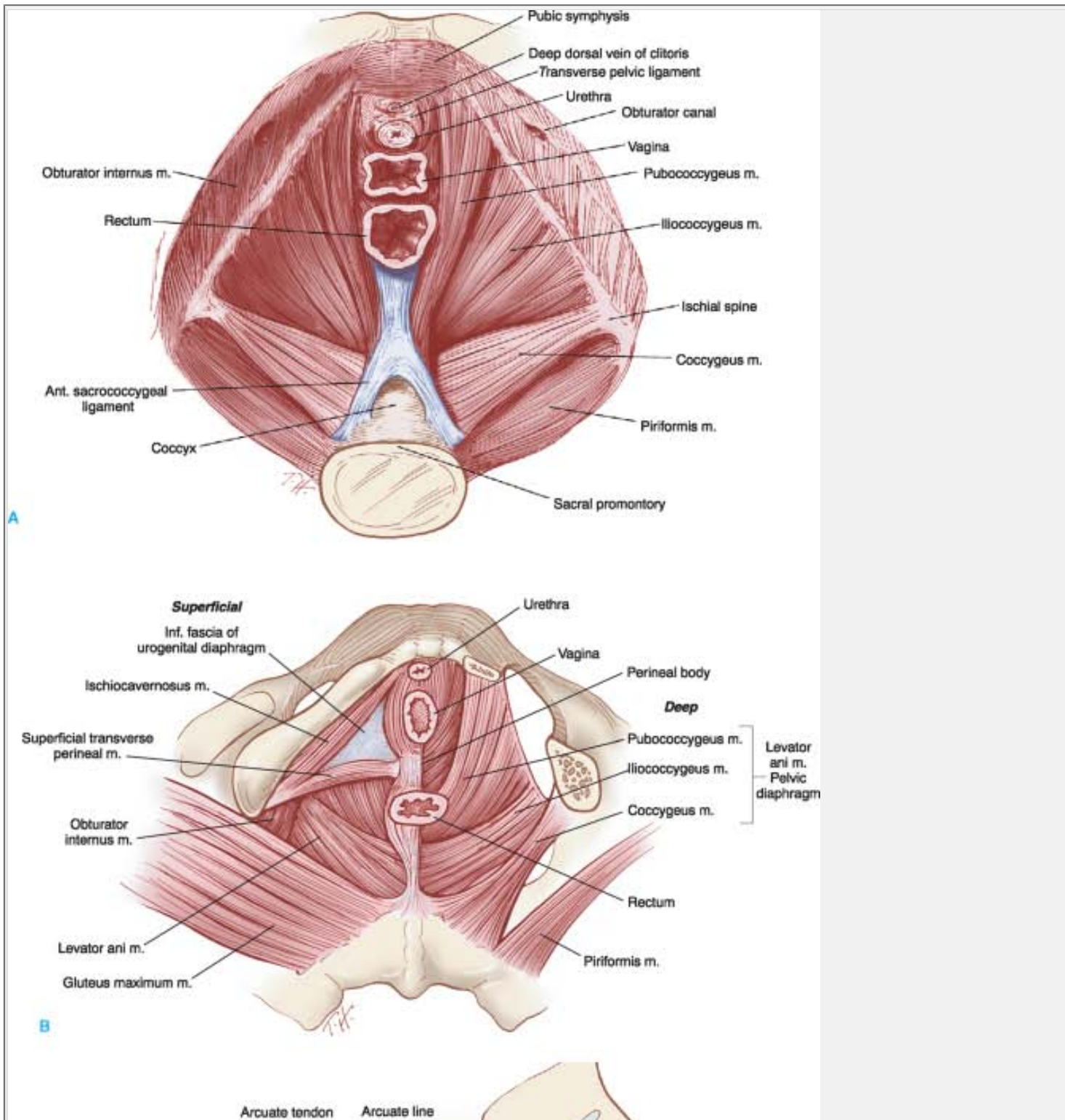
Lateral Wall

The muscles of the lateral pelvic wall pass into the gluteal region to assist in thigh rotation and adduction. They include the piriformis, the obturator internus, and the iliopsoas.

Pelvic Floor

Pelvic Diaphragm

The pelvic diaphragm is a funnel-shaped fibromuscular partition that forms the primary supporting structure for the pelvic contents (Fig. 5.4). It is composed of the levator ani and the coccygeus muscles, along with their superior and inferior fasciae (Table 5.1). It forms the ceiling of the ischiorectal fossa.



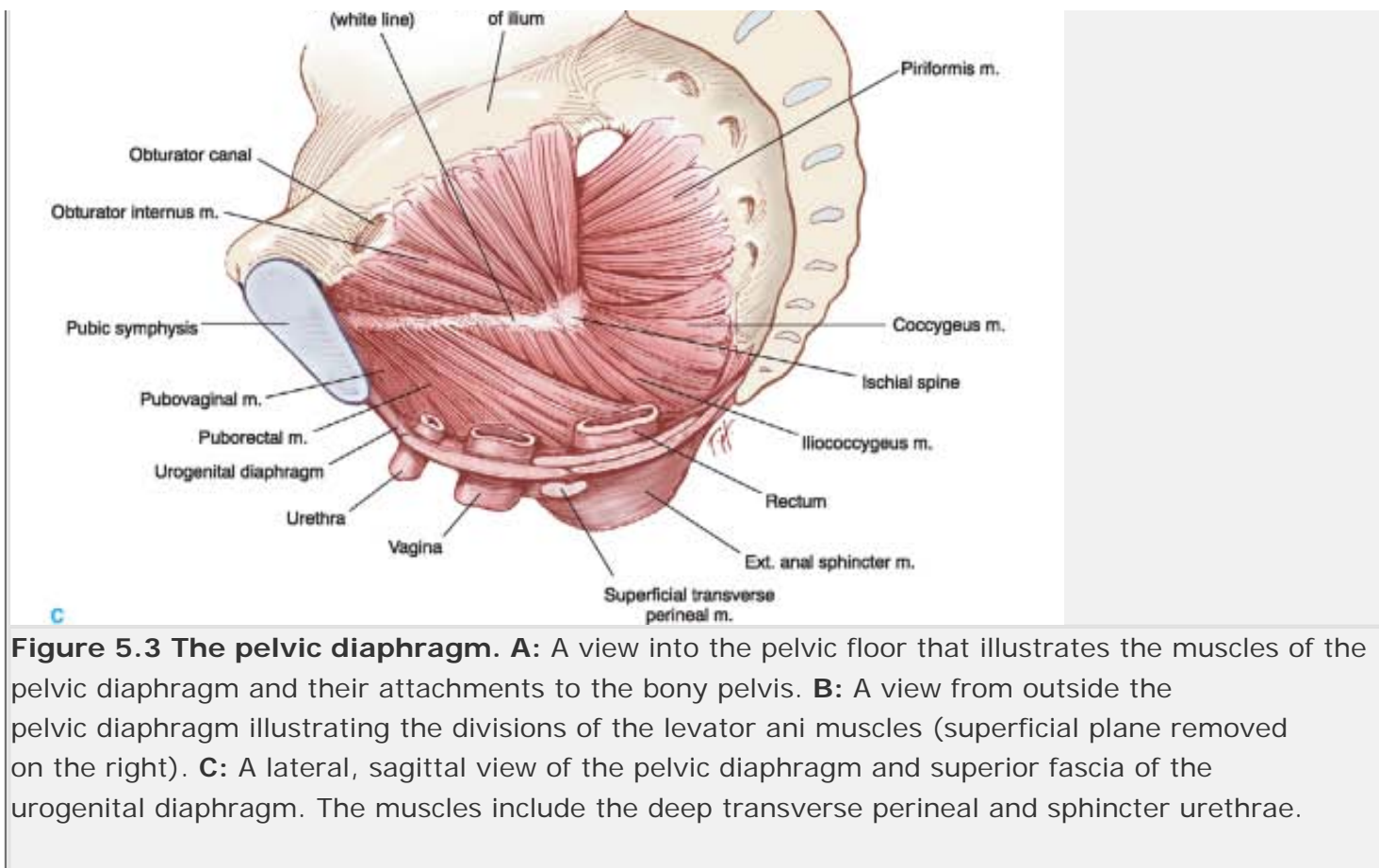


Figure 5.3 The pelvic diaphragm. A: A view into the pelvic floor that illustrates the muscles of the pelvic diaphragm and their attachments to the bony pelvis. **B:** A view from outside the pelvic diaphragm illustrating the divisions of the levator ani muscles (superficial plane removed on the right). **C:** A lateral, sagittal view of the pelvic diaphragm and superior fascia of the urogenital diaphragm. The muscles include the deep transverse perineal and sphincter urethrae.

Levator Ani

The levator ani muscles are composed of the pubococcygeus (including the pubovaginalis, pubourethralis, puborectalis, and the iliococcygeus). It is a broad, curved sheet of muscle stretching from the pubis anteriorly and the coccyx posteriorly, and from one side of the pelvis to the other. It is perforated by the urethra, vagina, and anal canal. Its origin is from the tendinous arch extending from the body of the pubis to the ischial spine. It is inserted into the central tendon of the perineum, the wall of the anal canal, the anococcygeal ligament, the coccyx, and the vaginal wall.

The levator ani assists the anterior abdominal wall muscles in containing the abdominal and pelvic contents. It supports the vagina, facilitates defecation, and aids

in maintaining fecal continence. During parturition, the levator ani supports the fetal head while the cervix dilates. The levator ani is innervated by S3 to S4, the inferior rectal nerve.

Urogenital Diaphragm

The muscles of the urogenital diaphragm reinforce the pelvic diaphragm anteriorly and are intimately related to the vagina and the urethra. They are enclosed between the inferior and superior fascia of the urogenital diaphragm. The muscles include the deep transverse perineal and sphincter urethrae (Table 5.1).

Table 5.1 Muscles of the Pelvic Floor				
	<i>Origin</i>	<i>Insertion</i>	<i>Action</i>	<i>Innervation</i>
Lateral Pelvic Wall				
<i>Piriformis</i>	Anterior aspect of S2–S4 and sacrotuberous ligament	Greater trochanter of the femur	Lateral rotation, abduction of thigh in flexion; holds head of femur in acetabulum	S1–S2; forms a muscular bed for the sacral plexus
<i>Obturator internus</i>	Superior and inferior pubic rami	Greater trochanter of the femur	Lateral rotation of thigh in flexion; assists in holding head of femur in acetabulum	(L5, S1) Obturator internus nerve
<i>Iliopsoas</i>	Psoas from the lateral margin of the lumbar vertebrae; iliacus from the iliac fossa	Lesser trochanter of the femur	Flexes thigh and stabilizes trunk on thigh; flexes vertebral column or bends it unilaterally	(L1–L3) Psoas-ventral rami of lumbar nerve (L2–L3) Iliacus-femoral nerve contains the lumbar plexus within its muscle body
Pelvic Floor				
Pelvic Diaphragm				

<i>Levator Ani</i> Pubococcygeus Pubovaginalis Puborectalis	From the tendinous arch, extending from the body of the pubis to the ischial spine	Central tendon of the perineum; wall of the anal canal; anococcygeal ligament; coccyx; vaginal wall	Assists the anterior abdominal wall muscles in containing the abdominal and pelvic contents; supports the posterior wall of the vagina; facilitates defecation; aids in fecal continence; during parturition, supports the fetal head during cervical dilation	S3–S4; the inferior rectal nerve
<i>Coccygeus</i>	Ischial spine and sacrospinous ligament	Lateral margin of the fifth sacral vertebra and coccyx	Supports the coccyx and pulls it anteriorly	S4–5
Urogenital Diaphragm				
<i>Deep transverse perineal</i>	Medial aspect of the ischiopubic rami	Lower part of the vaginal wall; anterior fibers blend with those of the sphincter urethrae	Steadies the central perineal tendon	S2–S4; perineal nerve
<i>Sphincter urethrae</i>	Medial aspect of the ischiopubic rami	Urethra and vagina	Compresses the urethra	S2–S4; perineal nerve

Blood Vessels

The pelvic blood vessels supply genital structures as well as the following:

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Urinary and gastrointestinal tracts

- Muscles of the abdominal wall, pelvic floor and perineum, buttocks, and upper thighs

- Fasciae, other connective tissue, and bones

- Skin and other superficial structures.

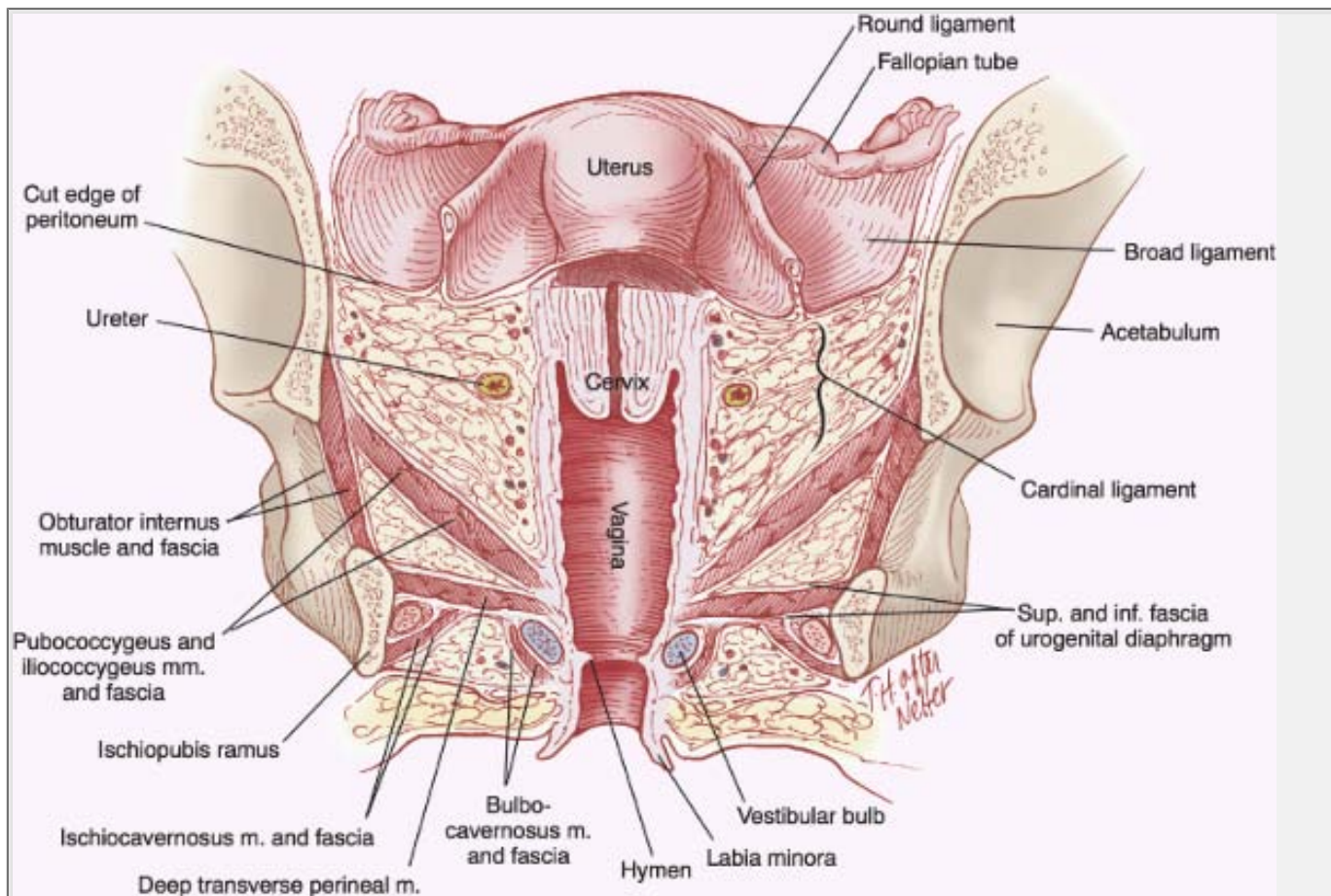


Figure 5.4 The ligaments and fascial support of the pelvic viscera.

Classically, vessels supplying organs are known as *visceral vessels* and those supplying

supporting structures are called *parietal vessels*.

Major Blood Vessels

The course of the major vessels supplying the pelvis is illustrated in Figure 5.5; their origin, course, branches, and venous drainage are presented in Table 5.2. In general, the venous system draining the pelvis closely follows the arterial supply and is named accordingly. Not infrequently, a vein draining a particular area may form a plexus with multiple channels. Venous systems, which are paired, mirror each other in their drainage patterns, with the notable exception of the ovarian veins. Unusual features of venous drainage are also listed in Table 5.2.

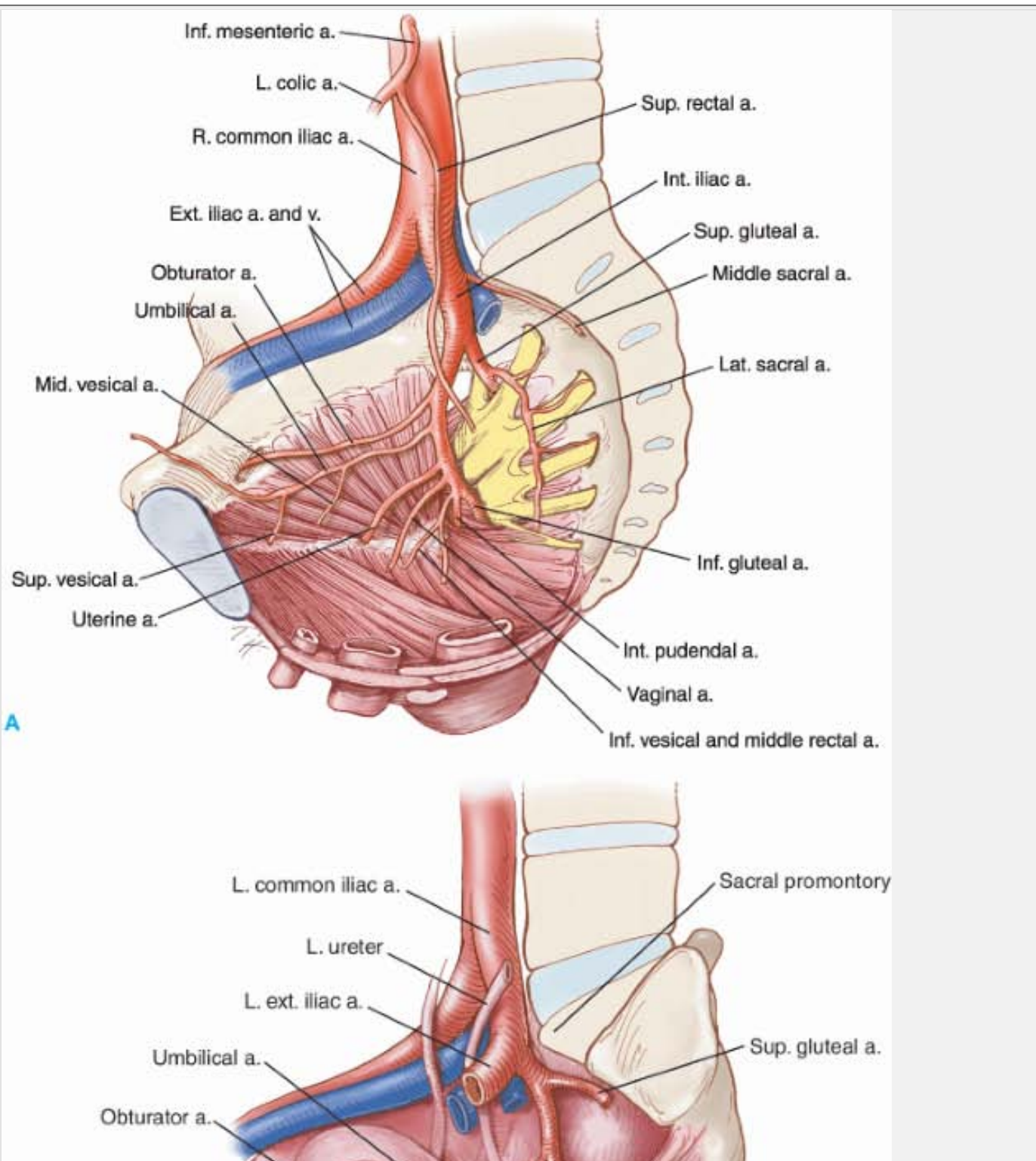
General Principles

"Control blood supply" and "maintain meticulous hemostasis" are two of the most common exhortations to young surgeons. In developing familiarity with the pattern of blood flow in the pelvis, several unique characteristics of this vasculature should be understood because of their potential implications to surgical practice:

- **The pelvic vessels play an important role in pelvic support.** They provide condensations of endopelvic fascia that act to reinforce the normal position of pelvic organs (5).
- **There is significant anatomic variation between individuals in the branching pattern of the internal iliac vessels.** There is no constant order in which branches divide from the parent vessel; some branches may arise as common trunks or may spring from other branches rather than from the internal iliac. Occasionally, a branch may arise from another vessel entirely (e.g., the obturator artery may arise from the external iliac or inferior epigastric artery). This variation may also be found in the branches of other major vessels; the ovarian arteries have been reported to arise from the renal arteries or as a common trunk from the front of the aorta on occasion. The inferior gluteal artery may originate from the posterior or the anterior branch of the internal iliac (hypogastric) artery (2). Patterns of blood flow may be asymmetric from side to side, and structures supplied by anastomoses of different vessels may show variation from person to person in proportion of vascular support provided by the vessels involved. The pelvic surgeon must be prepared for deviations

from "textbook" vascular patterns.

- **The pelvic vasculature is a high-volume, high-flow system with enormous expansive capabilities throughout reproductive life.** Blood flow through the uterine arteries increases to about 500 mL/min in late pregnancy. In nonpregnant women, certain conditions, such as uterine fibroids or malignant neoplasms, may be associated with neovascularization and hypertrophy of existing vessels and a corresponding increase in pelvic blood flow. Understanding of the volume and flow characteristics of the pelvic vasculature in different clinical situations will enable the surgeon to anticipate problems and take appropriate preoperative and intraoperative measures (including blood and blood product availability) to prevent or manage hemorrhage.
- **The pelvic vasculature is supplied with an extensive network of collateral connections (Fig. 5.6) that provides a rich anastomotic communication between different major vessel systems.** This degree of redundancy is important to ensure adequate supply of oxygen and nutrients in the event of major trauma or other vascular compromise. Hypogastric artery ligation continues to be used as a strategy for management of massive pelvic hemorrhage when other measures have failed. Bilateral hypogastric artery ligation, particularly when combined with ovarian artery ligation, dramatically reduces pulse pressure in the pelvis, converting flow characteristics from that of an arterial system to a venous system and allowing use of collateral channels of circulation to continue blood supply to pelvic structures. The significance of collateral blood flow is demonstrated by reports of successful pregnancies occurring after bilateral ligation of both hypogastric and ovarian arteries (6). Table 5.3 lists the collateral channels of circulation in the pelvis.



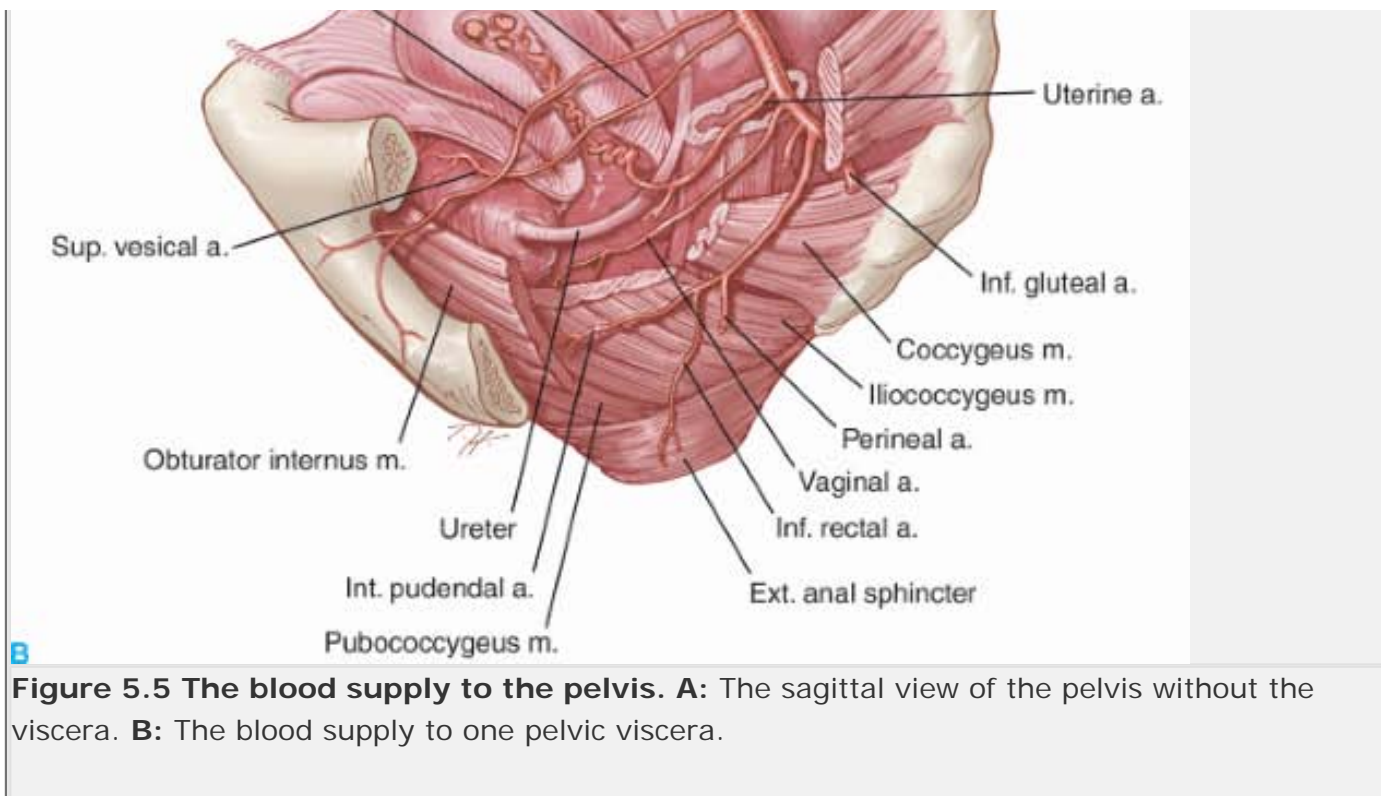


Figure 5.5 The blood supply to the pelvis. A: The sagittal view of the pelvis without the viscera. **B:** The blood supply to one pelvic viscera.

Table 5.2 The Major Blood Vessels of the Pelvis

<i>Artery</i>	<i>Origin</i>	<i>Course</i>	<i>Branches</i>	<i>Venous Drainage</i>
Ovarian	Arises from ventral surface of aorta just below the origin of the renal vessels	Crosses over common iliac vessels; in proximity to ureter over much of its course, crosses over ureter while superficial to the psoas muscle and runs just lateral to the ureter when entering the pelvis as part of the infundibulopelvic	To ovaries, fallopian tubes, broad ligament; often small branches to ureter	Right side drains into the inferior vena cava; left drains into the left renal vein

ligament				
Inferior mesenteric artery (IMA)	Unpaired left-sided retroperitoneal artery arising from the aorta 2–5 cm proximal to its bifurcation	IMA and its branches pass over the left psoas muscle and common iliac vessels; IMA courses anterior to the ureter and ovarian vessels above the pelvic brim	<ol style="list-style-type: none"> 1. <i>Left colic</i>—originates above pelvic brim; supplies left transverse colon, splenic flexure, descending colon 2. <i>Sigmoid</i>—several branches; supply sigmoid colon 3. <i>Superior rectal (hemorrhoidal)</i>—divides into two terminal branches to supply rectum 	Inferior mesenteric vein empties into the splenic vein
Common iliac artery	Terminal division of the aorta at fourth lumbar vertebra	Oblique and lateral course, about 5 cm in length	<ol style="list-style-type: none"> 1. <i>External iliac</i> 2. <i>Internal iliac</i> 	Lie posterior and slightly medial to arteries; drain into inferior vena cava
External iliac femoral artery	Lateral bifurcation of common iliac, opposite the lumbosacral joint	Along the medial border of the psoas muscle and lateral pelvic side wall; becomes femoral artery after passing under the inguinal ligament to supply lower extremity	<ol style="list-style-type: none"> 1. <i>Superficial epigastric</i>—supplies skin and subcutaneous tissue of lower anterior abdominal wall 2. <i>External pudendal</i>—supplies skin and subcutaneous tissue of mons pubis and anterior vulva 3. <i>Superficial circumflex iliac</i>—supplies skin/subcutaneous tissues of the flank 4. <i>Inferior epigastric</i>—supplies musculofascial layer of lower anterior abdominal wall 5. <i>Deep circumflex iliac</i>—supplies musculofascial layer 	Lie posterior and then medial to the artery as it enters the anterior thigh; drain into common iliac veins

Internal iliac (hypogastric) artery	Medial bifurcation of common iliac artery, begins opposite the lumbosacral joint; is major blood supply to the pelvis	Descends sharply into the pelvis; divides into an anterior and posterior division 3–4 cm after origin	<p><i>Posterior division</i></p> <ol style="list-style-type: none"> 1. <i>Iliolumbar</i>—anastomoses with lumbar and deep circumflex iliac arteries; helps supply lower abdominal wall, iliac fossa 2. <i>Lateral sacral</i>—supplies contents of sacral canal, piriformis muscle 3. <i>Superior gluteal</i>—supplies gluteal muscles 	Deep to arteries, from complex plexus; drain into common iliac veins
			<p><i>Anterior division:</i></p> <ol style="list-style-type: none"> 1. <i>Obturator</i>—supplies iliac fossa, posterior pubis, obturator internus muscle 2. <i>Internal pudendal</i> 3. <i>Umbilical</i>—remnant of fetal umbilical artery; after giving off branches, as the medial umbilical ligament 4. <i>Superior, middle, inferior vesical</i>—supply bladder and one or more branches to the ureter 5. <i>Middle rectal (hemorrhoidal)</i>—supplies rectum, branches to midvagina 6. <i>Uterine</i>—supplies uterine corpus and cervix, with branches to upper vagina. 	

			tube, round ligament, and ovary	
			7. <i>Vaginal</i> —supplies vagina	
			8. <i>Inferior gluteal</i> —supplies gluteal muscles, muscles of posterior thigh	
Internal pudendal artery	Internal iliac artery; provides the major blood supply to the perineum	Leaves the pelvis through the greater sciatic foramen, courses around the ischial spine, and enters the ischiorectal fossa through the lesser sciatic foramen. In its path to the perineum, lies with the pudendal nerve within Alcock's canal, a fascial tunnel over the obturator internus muscle	<ol style="list-style-type: none"> 1. <i>Inferior rectal (hemorrhoids)</i>—supplies anal canal, external anal sphincter, perianal skin, with branches to levator ani 2. <i>Perineal</i>—supplies perineal skin, muscles of superficial perineal compartment (bulbocavernosus, ischiocavernosus, superficial transverse perineal) 3. <i>Clitoral</i>—supplies clitoris, vestibular bulb, Bartholin gland, and urethra 	Drain into internal iliac veins
Middle sacral artery	Midline unpaired vessel arising from posterior terminal aorta	Courses over lower lumbar vertebrae, sacrum, and coccyx	Supplies bony and muscular structures of posterior pelvic wall	Paired middle sacral veins usually drain into left common iliac vein

Lumbar arteries	Segmental branches arising at each lumbar level from posterior aorta	Pass around the side of the 4 superior lumbar vertebrae, divide into anterior and posterior branches	Supplies abdominal wall musculature (external/internal oblique, transversus abdominis)	Veins into inferior vena cava
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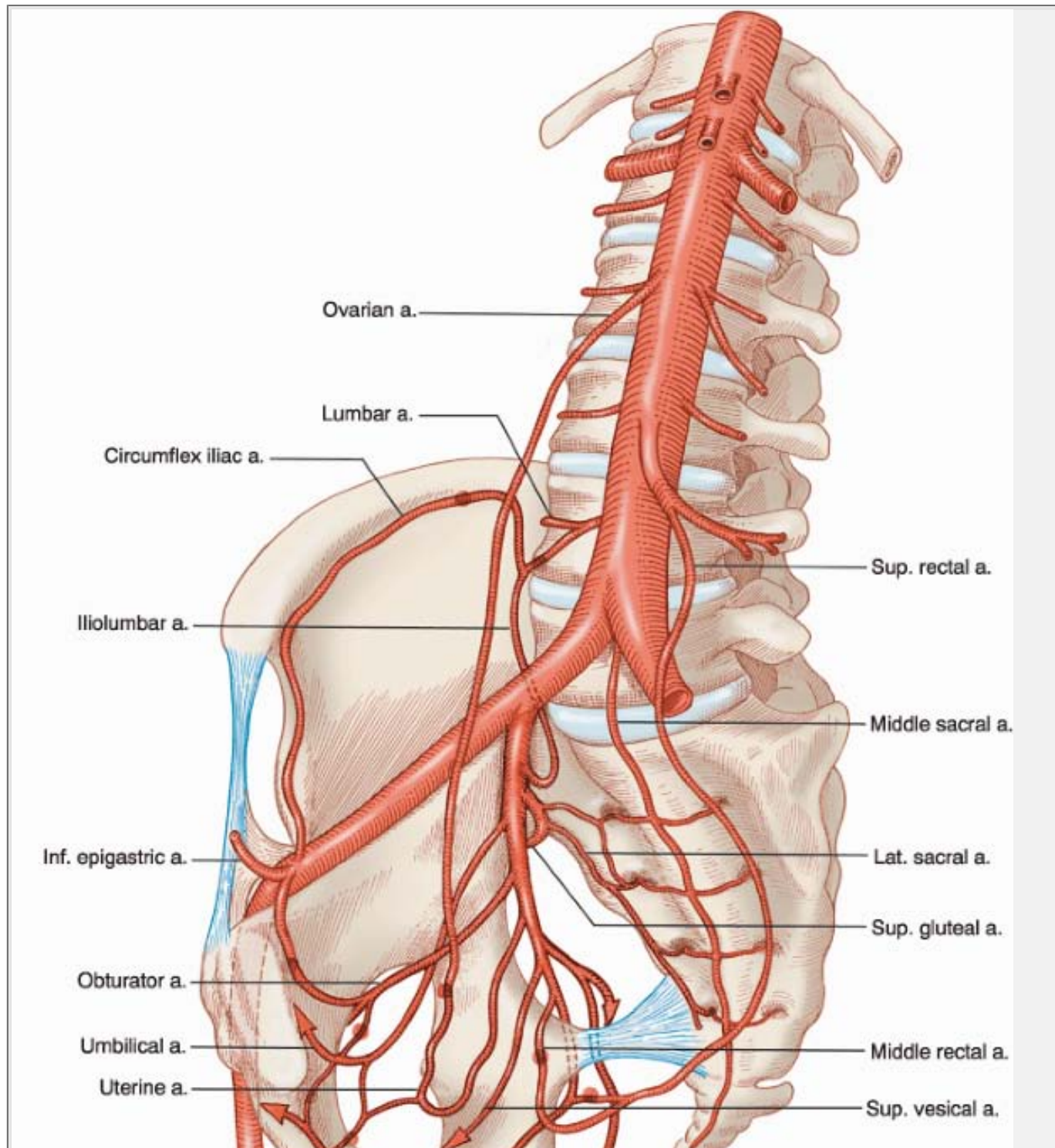
Special Vascular Considerations

To avoid injury to vascular structures and resultant hemorrhage while inserting a trocar into the anterior abdominal wall during laparoscopy, the surgeon should keep in mind certain anatomic relationships. The inferior epigastric artery is a branch of the external iliac artery, arising from the parent vessel at the medial border of the inguinal ligament and coursing cephalad lateral to and posterior to the rectus sheath at the level of the arcuate line. It lies about 1.5 cm lateral to the medial umbilical fold, which marks the site of the obliterated umbilical artery. The aortic bifurcation occurs at the level of L4 to L5, just above the sacral promontory. Palpation of the sacral promontory to guide trocar insertion allows the surgeon to avoid the major vascular structures in this area (see Fig. 21.4 in Chapter 21).

Lymphatics

The pelvic lymph nodes are generally arranged in groups or chains and follow the course of the larger pelvic vessels, for which they are usually named. Smaller nodes that lie close to the visceral structures are usually named for those organs. Lymph nodes in the pelvis receive afferent lymphatic vessels from pelvic and perineal visceral and parietal structures and send efferent lymphatics to more proximal nodal groups. The number of lymph nodes and their exact location is variable; however, certain nodes tend to be relatively constant:

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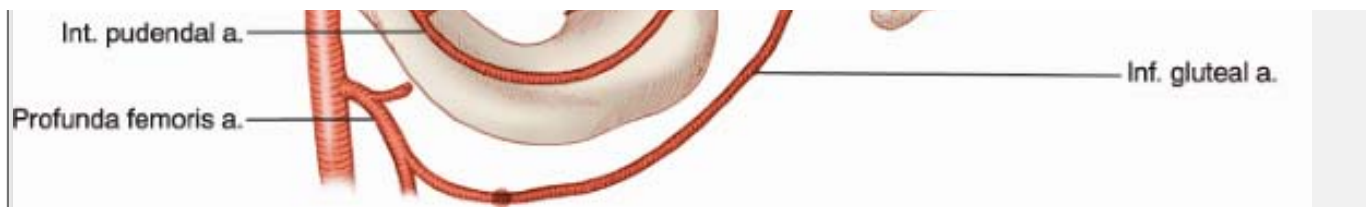


Figure 5.6 The collateral blood vessels of the pelvis. (Modified from **Kamina P.** *Anatomie gynécologique et obstétricale*. Paris, France: Maloine Sa Éditeur, 1984:125, with permission.)

- Obturator node in the obturator foramen, close to the obturator vessels and nerve
- Nodes at the junction of the internal and external iliac veins
- Ureteral node in the broad ligament near the cervix, where the uterine artery crosses over the ureter
- The *Cloquet* or Rosenmüller node—the highest of the deep inguinal nodes that lies within the opening of the femoral canal

Table 5.3 Collateral Arterial Circulation of the Pelvis	
Primary Artery	Collateral Arteries
Aorta	
Ovarian artery	Uterine artery
Superior rectal artery (inferior mesenteric artery)	Middle rectal artery Inferior rectal artery (internal pudendal)
Lumbar arteries	Iliolumbar artery
Vertebral arteries	Iliolumbar artery
Middle sacral artery	Lateral sacral artery
External Iliac	
Deep iliac circumflex artery	Iliolumbar artery

Inferior epigastric artery	Superior gluteal artery Obturator artery
<i>Femoral</i>	
Medial femoral circumflex artery	Obturator artery Inferior gluteal artery
Lateral femoral circumflex artery	Superior gluteal artery Iliolumbar artery

Figure 5.7 illustrates the pelvic lymphatic system. Table 5.4 outlines the major lymphatic chains of relevance to the pelvis and their primary afferent connections from major pelvic and perineal structures. There are extensive interconnections between lymph vessels and nodes; more than one lymphatic pathway is usually available for drainage of each pelvic site. Bilateral and crossed extension of lymphatic flow may occur, and entire groups of nodes may be bypassed to reach more proximal chains.

The natural history of most genital tract malignancies directly reflects the lymphatic drainage of those structures, although the various interconnections, different lymphatic paths, and individual variability make the spread of malignancy somewhat unpredictable. Regional lymph node metastasis is one of the most important factors in formulation of treatment plans for gynecologic malignancies and prediction of eventual outcome.

Nerves

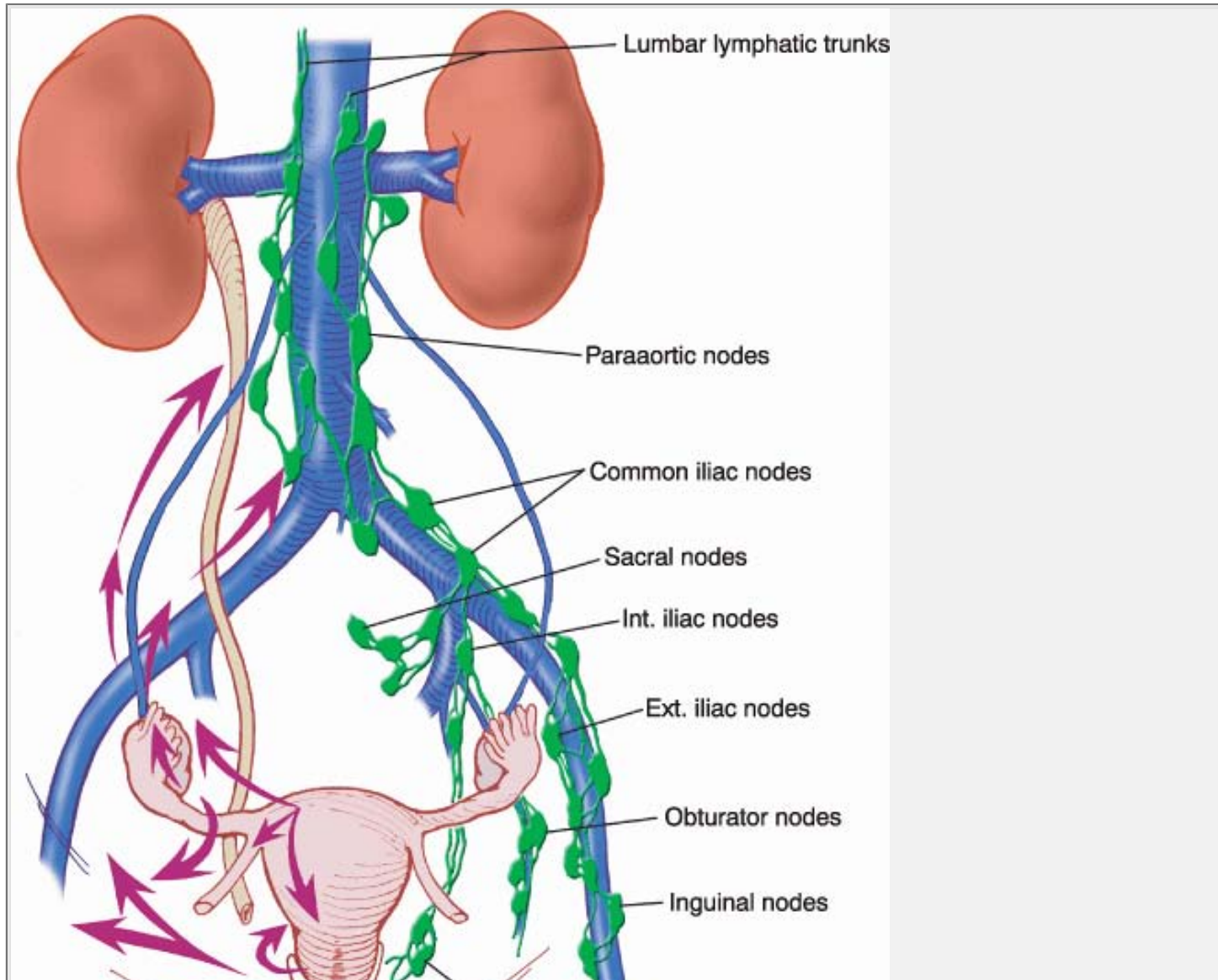
The pelvis is innervated by both the autonomic and somatic nervous systems. The autonomic nerves include both *sympathetic* (adrenergic) and *parasympathetic* (cholinergic) fibers and provide the primary innervation for genital, urinary, and gastrointestinal visceral structures and blood vessels.

Somatic Innervation

The *lumbosacral plexus* (Fig. 5.8) and its branches provide motor and sensory somatic innervation to the lower abdominal wall, the pelvic and urogenital diaphragms, the perineum, and the hip and lower extremity. The nerves originating from the muscles, the lumbosacral trunk, the anterior divisions of the upper four sacral nerves (*sacral plexus*), and the anterior division of the coccygeal nerve and fibers from the fourth and

fifth sacral nerves (*coccygeal plexus*) are found on the anterior surface of the piriformis muscle and

lateral to the coccyx, respectively, deep in the posterior pelvis. In Table 5.5 each major branch is listed by spinal segment and structures innervated. In addition to these branches, the lumbosacral plexus includes nerves that innervate muscles of the lateral pelvic wall (obturator internus, piriformis), posterior hip muscles, and the pelvic diaphragm. A visceral component, the pelvic splanchnic nerve, also is included.



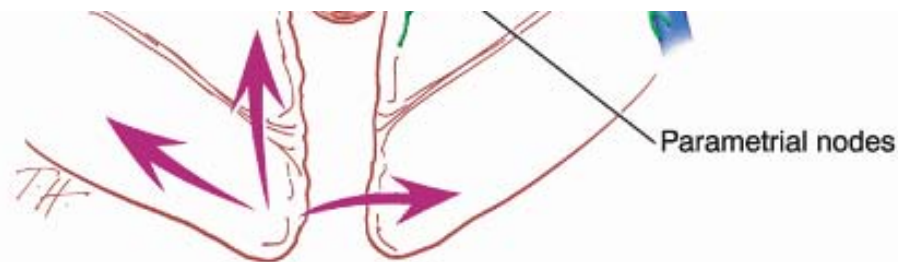


Figure 5.7 The lymphatic drainage of the female pelvis. The vulva and lower vagina drain to the superficial and deep inguinal nodes, sometimes directly to the iliac nodes (along the dorsal vein of the clitoris) and to the other side. The cervix and upper vagina drain laterally to the parametrial, obturator, and external iliac nodes and posteriorly along the uterosacral ligaments to the sacral nodes. Drainage from these primary lymph node groups is upward along the infundibulopelvic ligament, similar to drainage of the ovary and fallopian tubes to the paraaortic nodes. The lower uterine body drains in the same manner as the cervix. Rarely, drainage occurs along the round ligament to the inguinal nodes.

Nerves supplying the cutaneous aspects of the anterior, medial, and lateral lower extremities, as well as the deep muscles of the anterior thigh, primarily leave the pelvis by passing beneath the inguinal ligament. Nerves supporting the posterior cutaneous and deep structures of the hip, thigh, and leg lie deep in the pelvis and should not be vulnerable to injury during pelvic surgery. **The obturator nerve travels along the lateral pelvic wall to pass through the obturator foramen into the upper thigh, and it may be encountered in more radical dissections involving the lateral pelvic wall and in paravaginal repairs.**

Table 5.4 Primary Lymph Node Groups Providing Drainage to Genital Structures

Nodes	Primary Afferent Connections
Aortic/paraaortic	Ovary, fallopian tube, uterine corpus (upper); drainage from common iliac nodes
Common iliac	Drainage from external and internal iliac nodes
External iliac	Upper vagina, cervix, uterine corpus (upper); drainage from inguinal
Internal iliac	Upper vagina, cervix, uterine corpus (lower)
Lateral sacral	
Superior gluteal	
Inferior gluteal	
Obturator	
Vesical	
Rectal	
Parauterine	
Inguinal	Vulva, lower vagina; (rare: uterus, tube, ovary)
Superficial	
Deep	

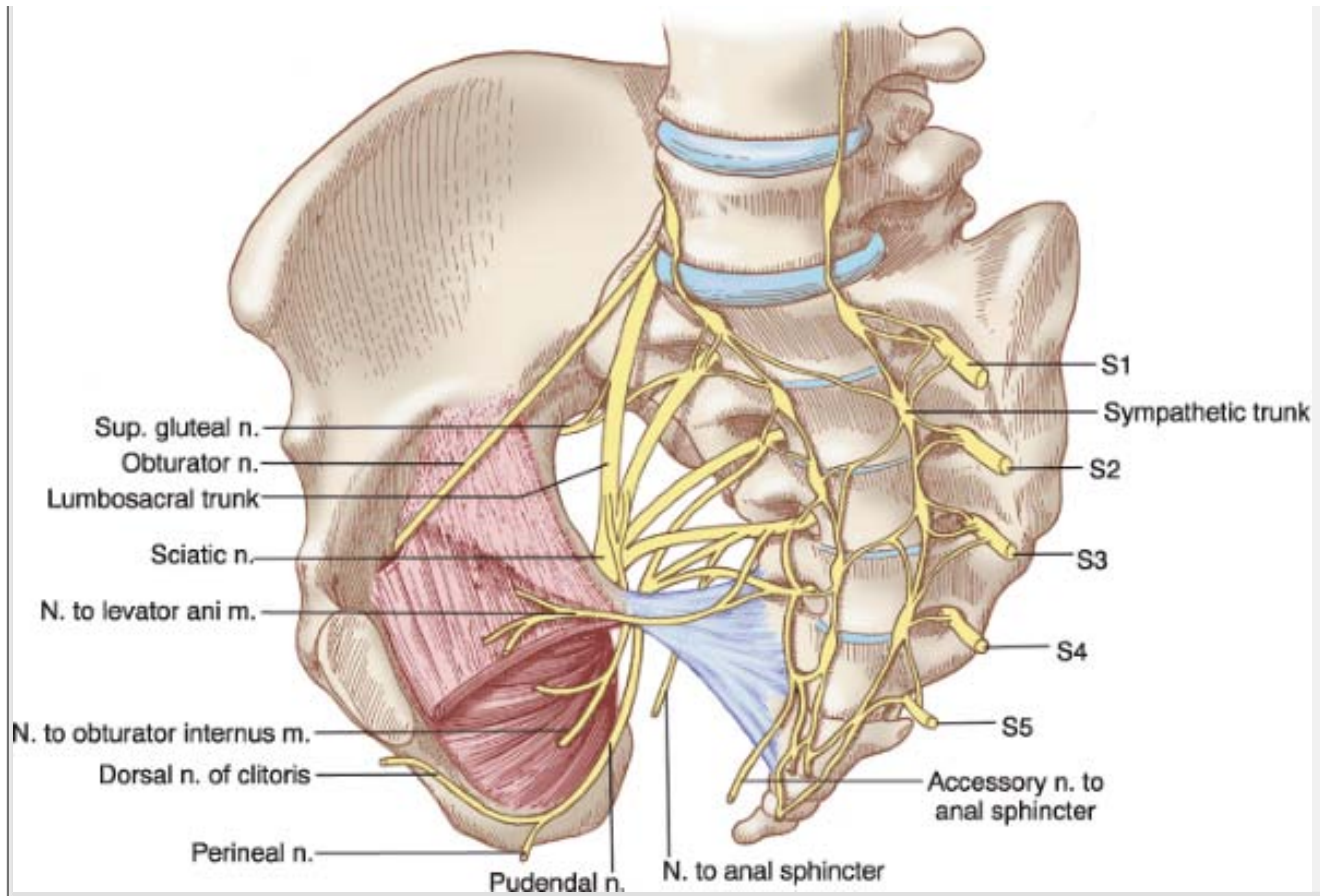


Figure 5.8 The sacral plexus. (Modified from **Kamina P.** *Anatomie gynécologique et obstétricale*. Paris, France: Maloine Sa Éditeur, 1984: 90, with permission.)

Table 5.5 Lumbosacral Plexus

Nerve	Spinal Segment	Innervation
Iliohypogastric	T12, L1	Sensory—skin near iliac crest, just above symphysis pubis
Ilioinguinal	L1	Sensory—upper medial thigh, mons, labia majora
Lateral femoral cutaneous	L2, L3	Sensory—lateral thigh to level of knee
Femoral	L2, L3, L4	Sensory—anterior and medial thigh, medial leg and foot, hip and knee joints Motor—iliacus, anterior thigh muscles
Genitofemoral	L1, L2	Sensory—anterior vulva (genital branch), middle/upper anterior thigh (femoral branch)
Obturator	L2, L3, L4 Motor—adductor muscles of thigh	Sensory—medial thigh and leg, hip and knee joints
Superior gluteal	L4, L5, S1	Motor—gluteal muscles
Inferior gluteal	L4, L5, S1, S2	Motor—gluteal muscles
Posterior femoral cutaneous	S1, S2, S3	Sensory—vulva, perineum, posterior thigh
Sciatic	L4, L5, S1, S2, S3 Motor—posterior thigh muscle, leg and foot muscles	Sensory—much of leg, foot, lower-extremity joints
Pudendal	S2, S3, S4 Motor—external anal sphincter, perineal muscles, urogenital diaphragm	Sensory—perianal skin, vulva and perineum, clitoris, urethra, vaginal vestibule

The pudendal nerve crosses over the piriformis to travel with the internal pudendal vessels into the ischiorectal fossa, where it divides into its three terminal branches to provide the primary innervation to the perineum. Other nerves contribute to the cutaneous innervation of the perineum:

- **The anterior labial nerve branches of the ilioinguinal nerve**—these nerves emerge from within the inguinal canal and through the superficial inguinal ring to the mons and upper

labia majora.

- **The genital branch of the genitofemoral nerve**—this branch enters the inguinal canal with the round ligament and passes through the superficial inguinal ring to the anterior vulva.
 - **The perineal branches of the posterior femoral cutaneous nerve**—after leaving the pelvis through the greater sciatic foramen, these branches run in front of the ischial tuberosity to the lateral perineum and labia majora.
 - **Perforating cutaneous branches of the second and third sacral nerves**—these branches perforate the sacrotuberous ligament to supply the buttocks and contiguous perineum.
-
- **The anococcygeal nerves**—these nerves arise from S4 to S5 and also perforate the sacrotuberous ligament to supply the skin overlying the coccyx.

Autonomic Innervation

Functionally, the innervation of the pelvic viscera may be divided into an *efferent* component and an *afferent*, or sensory, component. In reality, however, afferent and efferent fibers are closely associated in a complex interlacing network and cannot be separated anatomically.

Efferent Innervation

Efferent fibers of the autonomic nervous system, unlike motor fibers in the somatic system, involve one synapse outside the central nervous system, with two neurons required to carry each impulse. In the *sympathetic (thoracolumbar) division*, this synapse is generally at some distance from the organ being innervated; conversely, the synapse is on or near the organ of innervation in the *parasympathetic (craniosacral) division*.

Axons from preganglionic neurons emerge from the spinal cord to make contact with

peripheral neurons arranged in aggregates known as *autonomic ganglia*. Some of these ganglia, along with interconnecting nerve fibers, form a pair of longitudinal cords called the *sympathetic trunks*. Located lateral to the spinal column from the base of the cranium to the coccyx, the sympathetic trunks lie along the medial border of the psoas muscle from T12 to the sacral prominence and then pass behind the common iliac vessels to continue into the pelvis on the anterior surface of the sacrum. On the anterolateral surface of the aorta, the *aortic plexus* forms a lacy network of nerve fibers with interspersed ganglia. Rami arising from or traversing the sympathetic trunks join this plexus and its subsidiaries.

The ovaries and part of the fallopian tubes and broad ligament are innervated by the *ovarian plexus*, a network of nerve fibers accompanying the ovarian vessels and derived from the aortic and renal plexuses. The *inferior mesenteric plexus* is a subsidiary of the *celiac plexus* and *aortic plexus* and is located along the inferior mesenteric artery and its branches, providing innervation to the left colon, sigmoid, and rectum.

The *superior hypogastric plexus (presacral nerve)* (Fig. 5.9) is the continuation of the aortic plexus beneath the peritoneum in front of the terminal aorta, the fifth lumbar vertebra, and the sacral promontory, medial to the ureters. Embedded in loose areolar tissue, the plexus overlies the middle sacral vessels and is usually composed of two or three incompletely fused trunks. It contains preganglionic fibers from lumbar nerves, postganglionic fibers from higher sympathetic ganglia and from the sacral sympathetic trunks, and visceral afferent fibers. Just below the sacral promontory, the superior hypogastric plexus divides into two loosely arranged nerve trunks, the *hypogastric nerves*. These nerves course inferiorly and laterally to connect with the inferior *hypogastric plexuses (pelvic plexuses)* (Fig. 5.9), which are a dense network of nerves and ganglia that lie along the lateral pelvic sidewall overlying branches of the internal iliac vessels.

The inferior hypogastric plexus includes efferent sympathetic fibers, afferent (sensory) fibers, and parasympathetic fibers arising from the pelvic splanchnic nerves (S2 to S4, *nervi erigentes*).

This paired plexus is the final common pathway of the pelvic visceral nervous system and is divided into three portions, representing distribution of innervation to the viscera:

- **Vesical plexus**

- Innervation: bladder and urethra

- Course: along vesical vessels

- **Middle rectal plexus (hemorrhoidal)**

- Innervation: rectum
- Course: along middle rectal vessels

- **Uterovaginal plexus (Frankenhäuser ganglion)**

- Innervation: uterus, vagina, clitoris, vestibular bulbs
- Course: along uterine vessels and through cardinal and uterosacral ligaments; sympathetic and sensory fibers derive from T10, L1; parasympathetic fibers derive from S2 to S4.

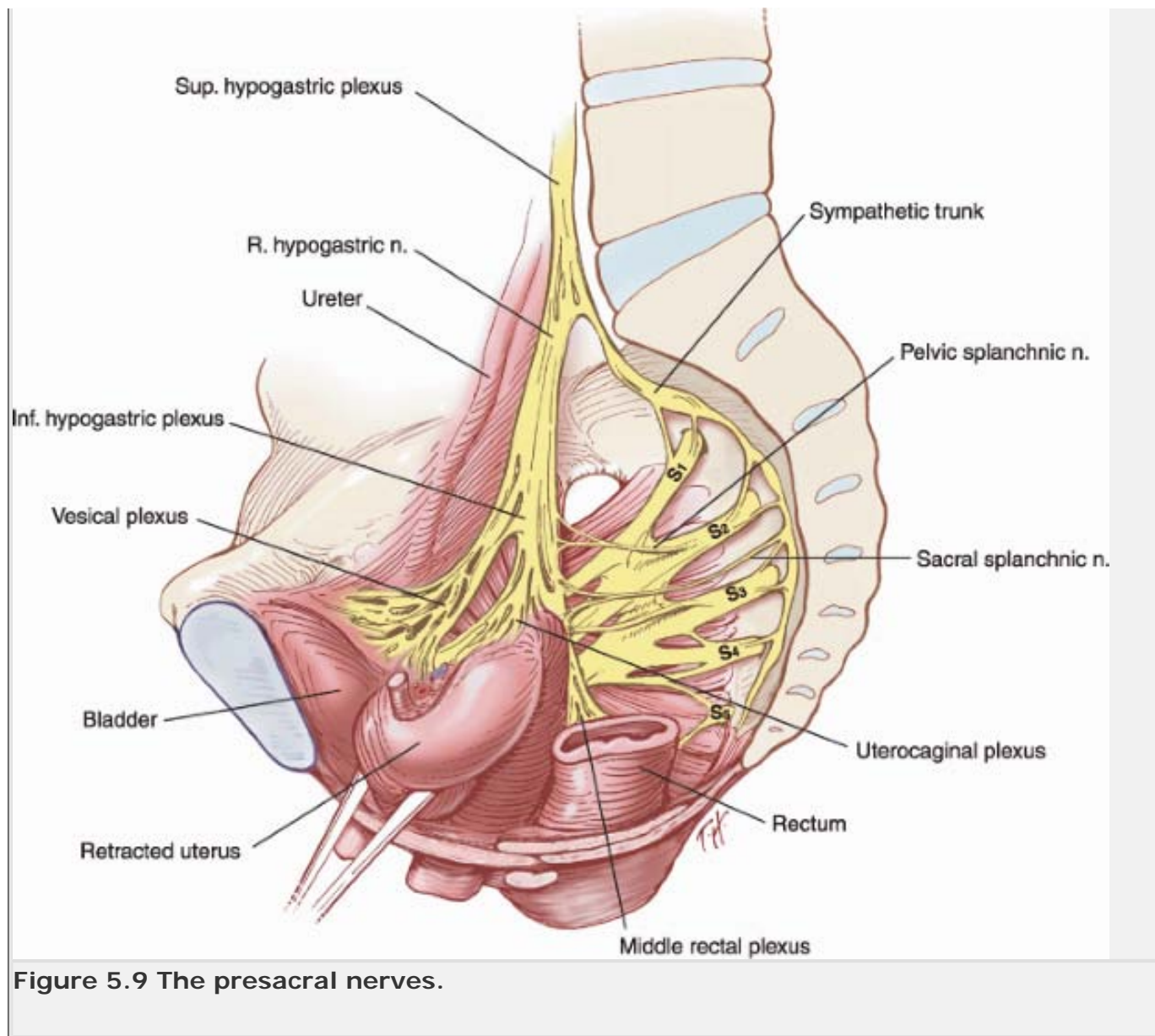


Figure 5.9 The presacral nerves.

Afferent Innervation

Afferent fibers from the pelvic viscera and blood vessels traverse the same pathways to provide sensory input to the central nervous system. They are also involved in reflex arcs needed for bladder, bowel, and genital tract function. The afferent fibers reach the central nervous system to have their first synapse within posterior spinal nerve ganglia.

Presacral neurectomy, in which a segment of the superior hypogastric plexus is divided and resected in order to interrupt sensory fibers from the uterus and cervix, has been associated with relief of dysmenorrhea secondary to endometriosis in about 50% to 75% of cases in which it has been used (7,8). Efferent fibers from the adnexa travel

with the ovarian plexus; thus, pain originating from the ovary or tube is not relieved by resection of the presacral nerve. Because this plexus also contains efferent sympathetic and parasympathetic nerve fibers intermixed with afferent fibers, disturbance in bowel or bladder function may result. An alternative surgical procedure advocated in recent years is resection of a portion of the uterosacral ligaments; because they contain numerous nerve fibers with more specific innervation to the uterus, it is postulated that bladder and rectal function is less vulnerable to compromise.

An anesthetic block of the pudendal nerve is performed most often for pain relief with uncomplicated vaginal deliveries but may also provide useful anesthesia for minor perineal surgical procedures. This nerve block may be accomplished transvaginally or through the perineum. A needle is inserted toward the ischial spine with the tip directed slightly posteriorly and through the sacrospinous ligament. As anesthetic agent is injected, frequent aspiration is required to avoid injection into the pudendal vessels, which travel with the nerve.

Pelvic Viscera

Embryonic Development

The female urinary and genital tracts are closely related, not only anatomically but also embryologically. Both are derived largely from primitive mesoderm and endoderm, and there is evidence that the embryologic urinary system has an important inductive influence on the developing genital system. **About 10% of infants are born with some abnormality of the genitourinary system, and anomalies in one system are often mirrored by anomalies in another system (9).**

Developmental defects may play a significant role in the differential diagnosis of certain clinical signs and symptoms and have special implications in pelvic surgery (9,10,11,12,13). Thus it is important for gynecologists to have a

basic understanding of embryology.

Following is a presentation of the urinary system, internal reproductive organs, and external genitalia in order of their initial appearance, although much of this development occurs concurrently. The development of each of these three regions proceeds synchronously at an early embryologic age (Table 5.6).

Urinary System

Kidneys, Renal Collecting System, Ureters

The kidneys, renal collecting system, and ureters derive from the longitudinal mass of mesoderm (known as the nephrogenic cord) found on each side of the primitive aorta. This process gives rise to three successive sets of increasingly advanced urinary structures, each developing more caudal to its predecessor.

The *pronephros*, or "first kidney," is rudimentary and nonfunctional; it is succeeded by the "middle kidney," or *mesonephros*, which is believed to function briefly before regressing. Although the *mesonephros* is transitory as an excretory organ, its duct, the *mesonephric (wolffian) duct*, is of singular importance for the following reasons:

- It grows caudally in the developing embryo to open, for the first time, an excretory channel into the primitive cloaca and the "outside world."
 - It serves as the starting point for development of the metanephros, which becomes the definitive kidney.
-
- It ultimately differentiates into the sexual duct system in the male.
 - Although regressing in female fetuses, there is evidence that the mesonephric duct may have an inductive role in development of the paramesonephric or müllerian duct (10).

Table 5.6. Development of Genital and Urinary Tracts by Embryologic Age		
Weeks of Gestation	Genital Development	Urinary Development
4-6	Urorectal septum	Pronephros
	Formation of cloacal folds, genital tubercle	Mesonephros/mesonephric duct
	Ureteric buds, metanephros	
	Genital ridges	Exstrophy of mesonephric ducts and ureters into bladder wall
6-7	End of indifferent phase of genital development	Major, minor calyces form
	Development of primitive sex cords	Kidneys begin to ascend
	Formation of paramesonephric ducts	
	Labioscrotal swellings	
8-11	Distal paramesonephric ducts begin to fuse	Kidney becomes functional
	Formation of sinuvaginal bulbs	
12	Development of clitoris and vaginal vestibule	
20	Canalization of vaginal plate	
32	Renal collecting duct system complete	

Development of the *metanephros* is initiated by the ureteric buds, which sprout from the distal mesonephric ducts; these buds extend cranially and penetrate the portion of the nephrogenic cord known as the *metanephric blastema*. The ureteric buds begin to branch sequentially, with each growing tip covered by metanephric blastema. The metanephric blastema ultimately form the renal functional units (the nephrons), whereas the ureteric buds become the collecting duct system of the kidneys (collecting tubules, minor and major calyces, renal pelvis) and the ureters. Although these primitive tissues differentiate along separate paths, they are interdependent on inductive influences from each other—neither can develop alone.

The kidneys initially lie in the pelvis but subsequently ascend to their permanent location, rotating almost 90 degrees in the process as the more caudal part of the embryo in effect grows away from them. Their blood supply, which first arises as branches of the middle sacral and common iliac arteries, comes from progressively higher branches of the aorta until the definitive renal arteries form; previous vessels then regress.

Bladder and Urethra

The cloaca forms as the result of dilation of the opening to the fetal exterior. The cloaca is partitioned by the mesenchymal urorectal septum into an anterior urogenital sinus and a posterior rectum. The bladder and urethra form from the most superior portion of the urogenital sinus, with surrounding mesenchyme contributing to their muscular and serosal layers. The remaining inferior urogenital sinus is known as the *phallic* or *definitive urogenital sinus*. Concurrently, the distal mesonephric ducts and attached ureteric

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buds are incorporated into the posterior bladder wall in the area that will become the bladder trigone. As a result of the absorption process, the mesonephric duct ultimately opens independently into the urogenital sinus below the bladder neck.

The *allantois*, which is a vestigial diverticulum of the hindgut that extends into the umbilicus and is continuous with the bladder, loses its lumen and becomes the fibrous band known as the *urachus* or *median umbilical ligament*. In rare instances, the urachal lumen remains partially patent, with formation of urachal cysts, or completely patent, with the formation of a urinary fistula to the umbilicus.

Genital System

Although genetic sex is determined at fertilization, the early genital system is indistinguishable between the two sexes in the embryonic stage. This is known as the "indifferent stage" of genital development, during which both male and female fetuses have gonads with prominent cortical and medullary regions, dual sets of genital ducts, and external genitalia that appear similar. Clinically, **sex is not apparent until about the twelfth week of embryonic life and depends on the elaboration of testis-determining factor and, subsequently, androgens by the male gonad.** Female development has been called the "basic developmental path of the human embryo," requiring not estrogen but the absence of testosterone.

Internal Reproductive Organs

The primordial germ cells migrate from the yolk sac through the mesentery of the hindgut to the posterior body wall mesenchyme at about the tenth thoracic level, which is the initial site of the future ovary (Figs. 5.10 and 5.11). Once the germ cells reach this

area, they induce proliferation of cells in the adjacent mesonephros and celomic epithelium to form a pair of *genital ridges* medial to the mesonephros. The development of the gonad is absolutely dependent on this proliferation because these cells form a supporting aggregate of cells (the primitive sex cords) that invest the germ cells and without which the gonad would degenerate.

Müllerian Ducts

The *paramesonephric or müllerian ducts* form lateral to the mesonephric ducts; they grow caudally and then medially to fuse in the midline. They contact the urogenital sinus in the region of the posterior urethra at a slight thickening known as the *sinusal tubercle*. Subsequent sexual development is controlled by the presence or absence of testis-determining factor, encoded on the Y chromosome and elaborated by the somatic sex cord cells. Testis-determining factor causes the degeneration of the gonadal cortex and differentiation of the medullary region of the gonad into Sertoli cells.

The Sertoli cells secrete a glycoprotein known as *anti-müllerian hormone (AMH)*, which causes regression of the paramesonephric duct system in the male embryo and is the likely signal for differentiation of Leydig cells from the surrounding mesenchyme. The Leydig cells produce testosterone and, with the converting enzyme 5 α -reductase, dihydrotestosterone. Testosterone is responsible for evolution of the mesonephric duct system into the vas deferens, epididymis, ejaculatory ducts, and seminal vesicle. At puberty, testosterone leads to spermatogenesis and changes in primary and secondary sex characteristics. Dihydrotestosterone triggers the development of the male external genitalia and the prostate and bulbourethral glands. In the absence of testis-determining factor, the medulla regresses, and the cortical sex cords break up into isolated cell clusters (the primordial follicles).

The germ cells differentiate into oogonia and enter the first meiotic division as primary oocytes, at which point development is arrested until puberty. In the absence of AMH, the mesonephric duct system degenerates, although in at least one fourth of adult women (11), remnants may be found in the mesovarium (*epoophoron, paroophoron*) or along the lateral wall of the uterus or vagina (*Gartner duct cyst*).

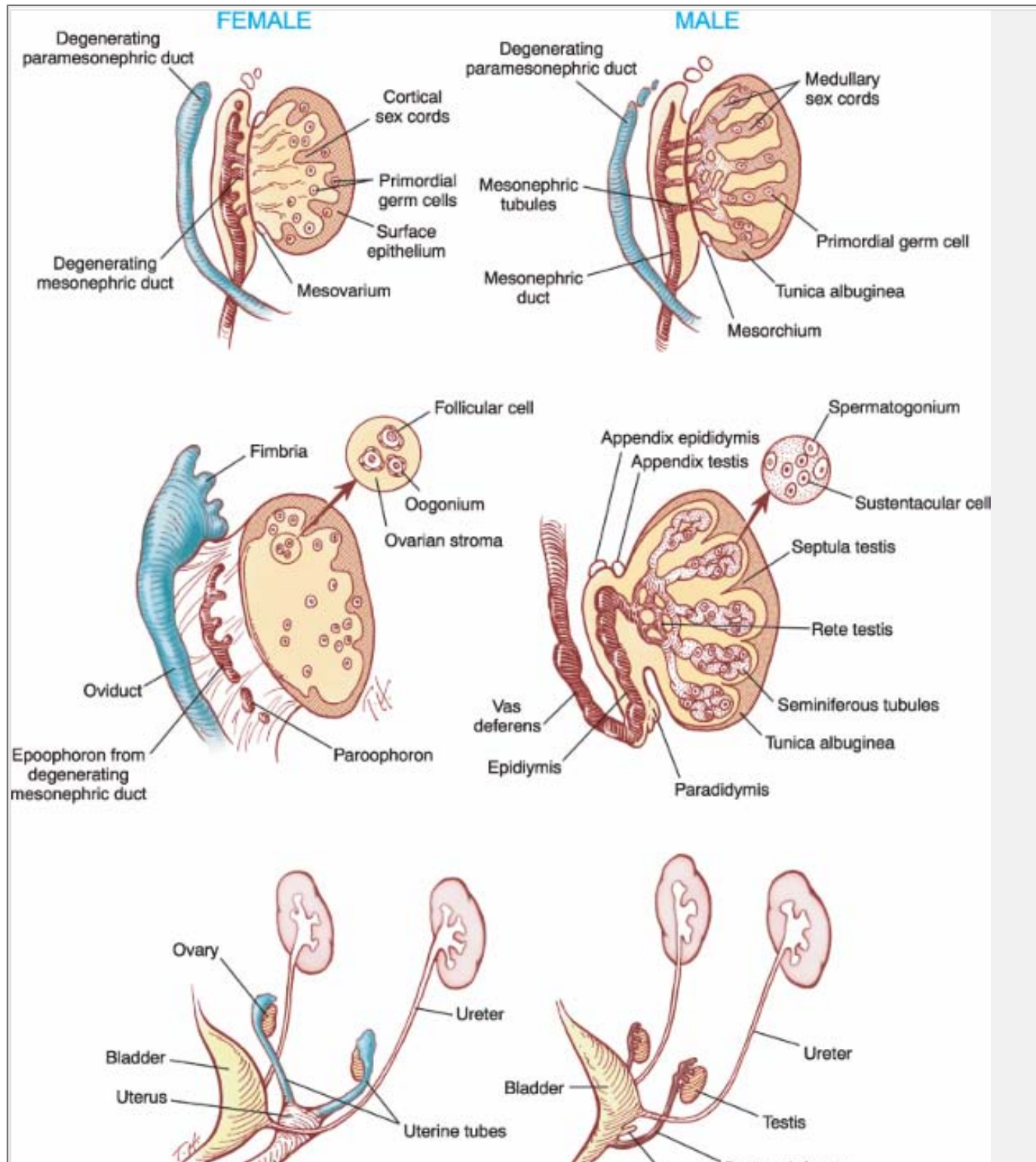




Figure 5.10 The comparative changes of the female and male during early embryonic development.

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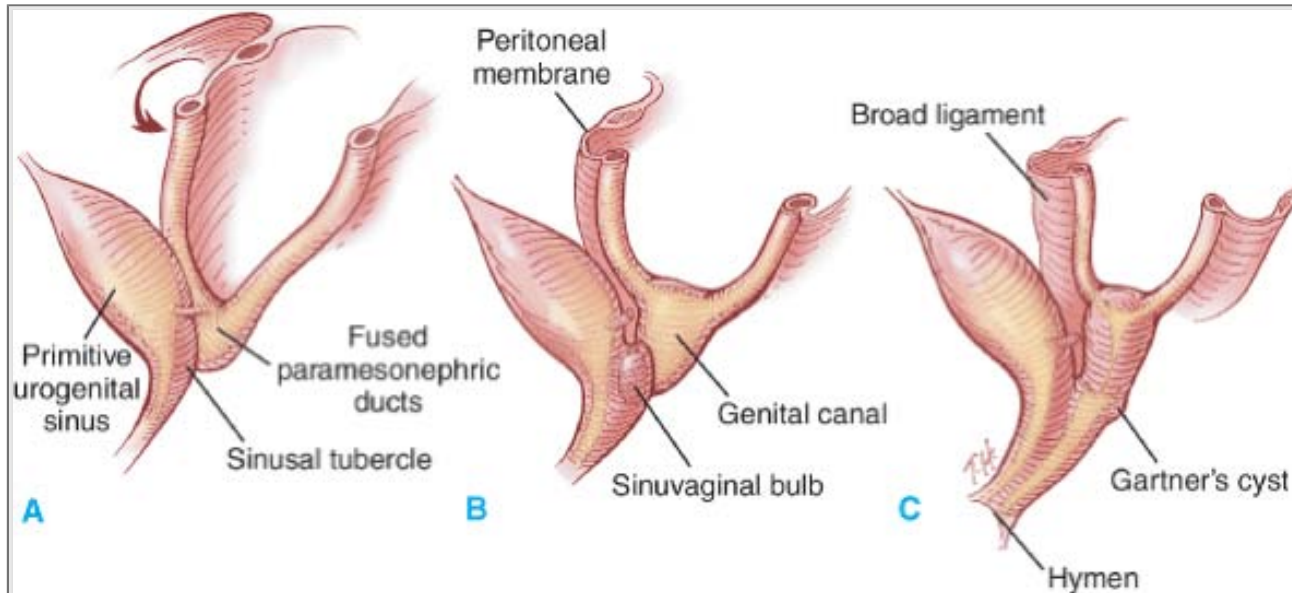


Figure 5.11 The embryonic development of the female genital tract. The formation of the uterus and vagina. **A:** The uterus and superior end of the vagina begin to form as the paramesonephric ducts fuse together near their attachment to the posterior wall of the primitive urogenital sinus. **B, C:** The ducts then zipper together in a superior direction between the third and fifth months. As the paramesonephric ducts are pulled away from the posterior body wall, they drag a fold of peritoneal membrane with them, forming the broad ligaments of the uterus. **A–C:** The inferior end of the vagina forms from the sinovaginal bulbs on the posterior wall of the primitive urogenital sinus.

The paramesonephric duct system subsequently develops. The inferior fused portion becomes the *uterovaginal canal*, which later becomes the epithelium and glands of the uterus and the upper vagina. The endometrial stroma and myometrium differentiate from

surrounding mesenchyme. The cranial unfused portions of the paramesonephric ducts open into the celomic (future peritoneal) cavity and become the *fallopian tubes*.

The fusion of the paramesonephric ducts brings together two folds of peritoneum, which become the broad ligament and divide the pelvic cavity into a posterior rectouterine and anterior vesicouterine pouch or cul-de-sac. Between the leaves of the broad ligament, mesenchyme proliferates and differentiates into loose areolar connective tissue and smooth muscle.

Vagina

The vagina forms in the third month of embryonic life. While the uterovaginal canal is forming, the endodermal tissue of the sinus tubercle begins to proliferate, forming a pair of *sinovaginal bulbs*, which become the inferior 20% of the vagina. The most inferior portion of the uterovaginal canal becomes occluded by a solid core of tissue (*the vaginal plate*), the origin of which is unclear. Over the subsequent 2 months, this tissue elongates and canalizes by a process of central desquamation, and the peripheral cells become the vaginal epithelium. The fibromuscular wall of the vagina originates from the mesoderm of the uterovaginal canal.

Accessory Genital Glands

The female accessory genital glands develop as outgrowths from the urethra (*paraurethral* or *Skene*) and the definitive urogenital sinus (*greater vestibular* or *Bartholin*). Although the ovaries first develop in the thoracic region, they ultimately arrive in the pelvis by a complicated process of descent. This descent by differential growth is under the control of a ligamentous cord called the *gubernaculum*, which is attached to the ovary superiorly and to the fascia in the region of the future labia majora inferiorly. The gubernaculum becomes attached to the paramesonephric ducts at their point of superior fusion so that it becomes divided into two separate structures. As the ovary and its mesentery (the mesovarium) are brought into the superior portion of the broad ligament,

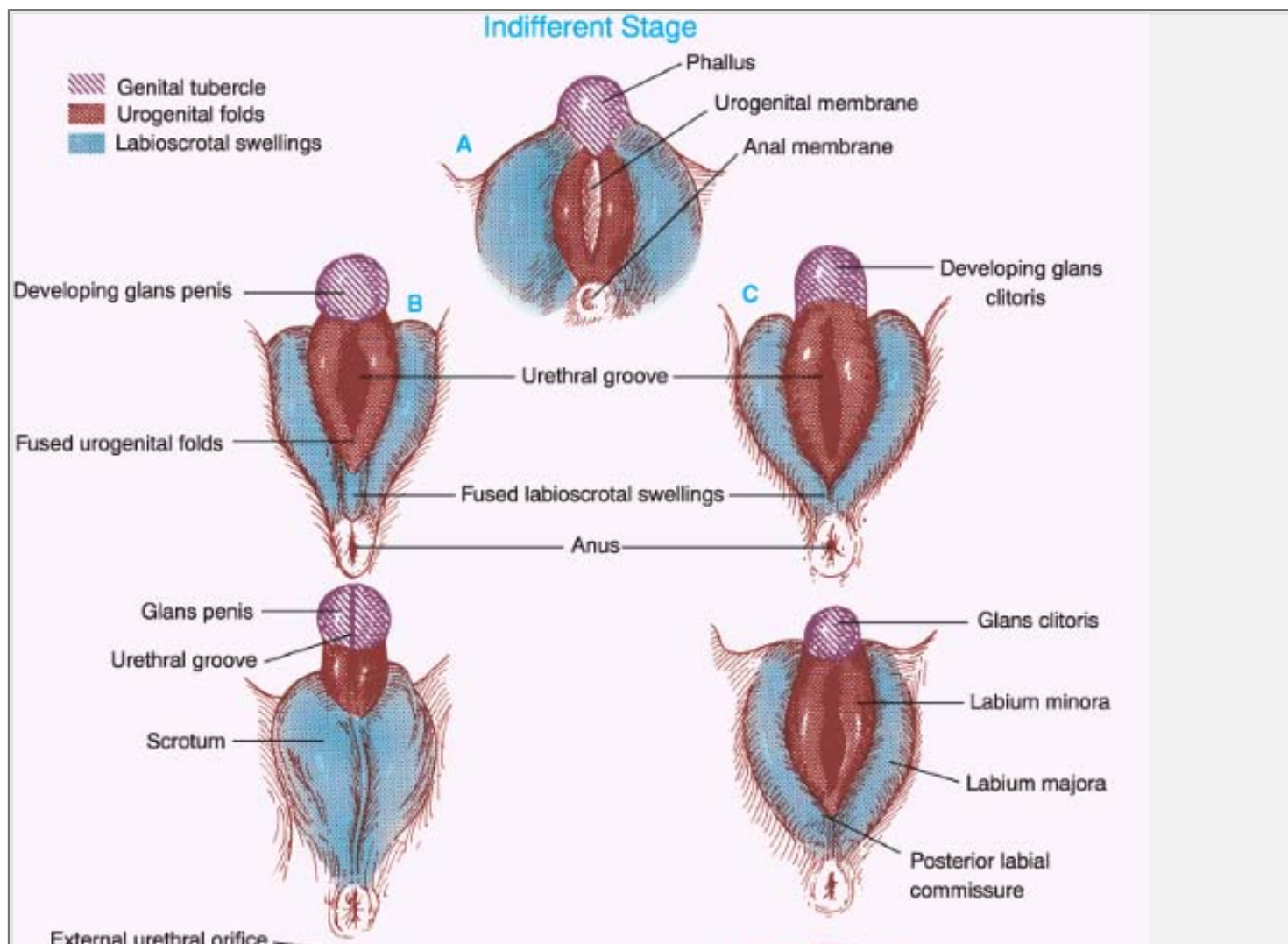
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the more proximal part of the gubernaculum becomes the *ovarian ligament*, and the distal gubernaculum becomes the *round ligament*.

External Genitalia

Early in the fifth week of embryonic life, folds of tissue form on each side of the cloaca

and meet anteriorly in the midline to form the **genital tubercle** (Fig. 5.12). With the division of the cloaca by the urorectal septum and consequent formation of the perineum, these cloacal folds are known anteriorly as the *urogenital folds* and posteriorly as the *anal folds*. The genital tubercle begins to enlarge. In the female embryo, its growth gradually slows to become the clitoris, and the urogenital folds form the labia minora. In the male embryo, the genital tubercle continues to grow to form the penis, and the urogenital folds are believed to fuse to enclose the penile urethra. Lateral to the urogenital folds, another pair of swellings develops, known in the indifferent stage as *labioscrotal swellings*. In the absence of androgens, they remain largely unfused to become the labia majora. The definitive urogenital sinus gives rise to the vaginal vestibule, into which open the urethra, vagina, and greater vestibular glands.



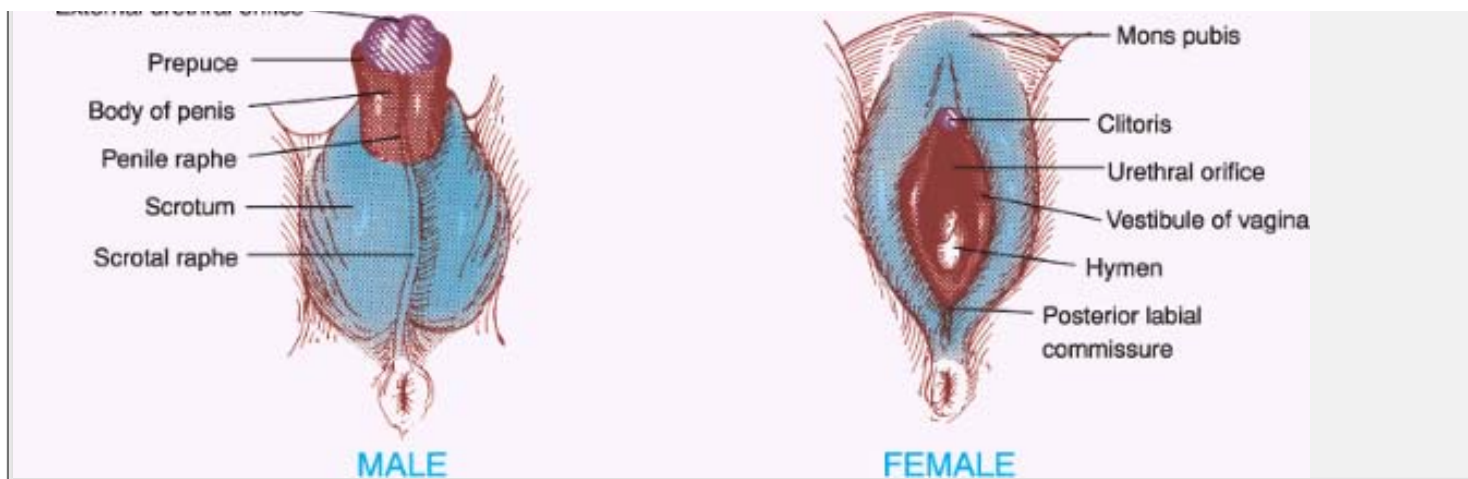


Figure 5.12 The comparative development of the female and male external genitalia. **A:** In both sexes, the development follows a uniform pattern through the seventh week and thereafter begins to differentiate. **B:** The male external genitalia. **C:** The female external genitalia.

Clinical Correlations

Developmental abnormalities of the urinary and genital systems can be explained and understood by a consideration of female and male embryologic development. Because of the intertwined development of these two systems, it is easy to understand how abnormalities in one may be associated with abnormalities in the other (12).

Urinary System

Urinary-tract anomalies arise from defects in the ureteric bud, the metanephric blastema, or their inductive interaction with each other.

Renal Agenesis

Renal agenesis occurs when one or both ureteric buds fail to form or degenerate, and the metanephric blastema is therefore not induced to differentiate into nephrons. Bilateral renal agenesis is incompatible with postnatal survival, but infants with only one kidney

usually survive, and the single kidney undergoes compensatory hypertrophy. Unilateral renal agenesis is often associated with absence or abnormality of fallopian tubes, uterus, or vagina—the paramesonephric duct derivatives.

Abnormalities of Renal Position

Abnormalities of renal position result from disturbance in the normal ascent of the kidneys. A malrotated pelvic kidney is the most common result; a horseshoe kidney, in which the kidneys are fused across the midline, occurs in about 1 in 600 individuals and also has a final position lower than usual because its normal ascent is prevented by the root of the inferior mesenteric artery.

Duplication of the Upper Ureter and Renal Pelvis

Duplication of the upper ureter and renal pelvis are relatively common and result from premature bifurcation of the ureteric bud. If two ureteric buds develop, there will be complete duplication of the collecting system. In this situation, one ureteric bud will open normally into the posterior bladder wall, and the second bud will be carried more distally within the mesonephric duct to form an ectopic ureteral orifice into the urethra, vagina, or vaginal vestibule; incontinence is the primary presenting symptom. Most of the aforementioned urinary abnormalities remain asymptomatic unless obstruction or infection supervenes. In that case, anomalous embryologic development must be included in the differential diagnosis.

Genital System

Because the early development of the genital system is similar in both sexes, congenital defects in sexual development, usually arising from a variety of chromosomal abnormalities, tend to present clinically with ambiguous external genitalia. These conditions are known as *intersex conditions* or *hermaphroditism* and are classified according to the histologic appearance of the gonads (see Chapter 24).

True Hermaphroditism

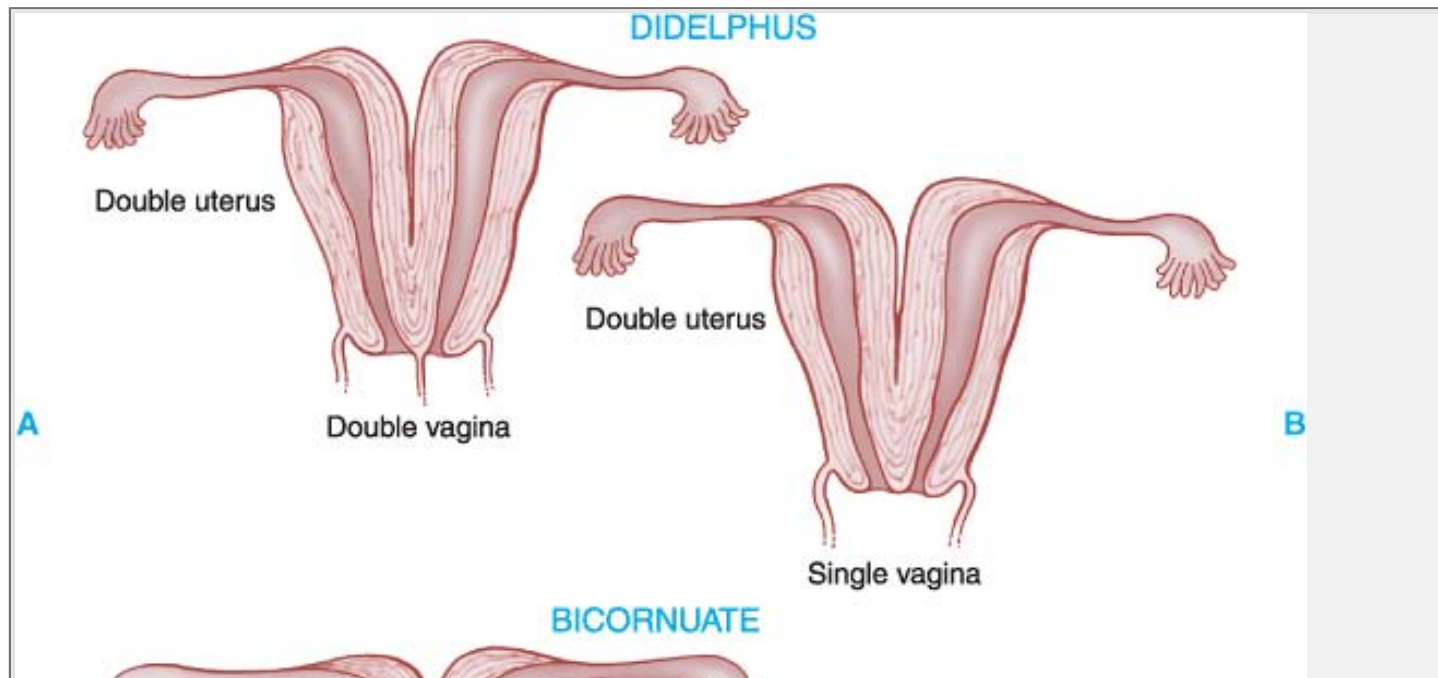
Individuals with true hermaphroditism have both ovarian and testicular tissue, most commonly as composite ovotestes but occasionally with an ovary on one side and a testis on the other. In the latter case, a fallopian tube and single uterine horn may develop

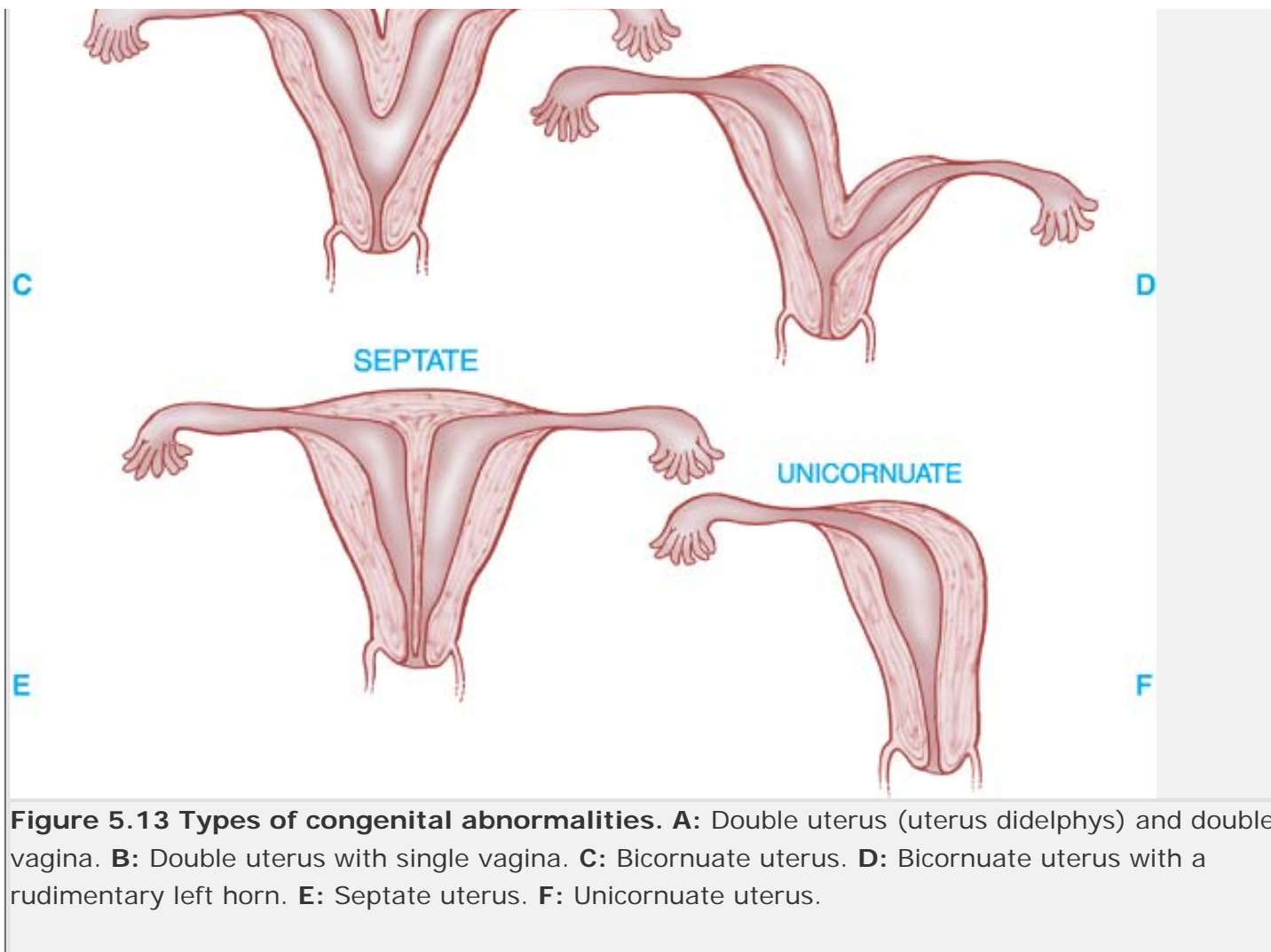
on the side with the ovary because of the absence of local AMH. True hermaphroditism is an extremely rare condition associated with chromosomal mosaicism, mutation, or abnormal cleavage involving the X and Y chromosomes.

Pseudohermaphroditism

In individuals with pseudohermaphroditism, the genetic sex indicates one sex, whereas the external genitalia has characteristics of the other sex. Males with pseudohermaphroditism are genetic males with feminized external genitalia, most commonly manifesting as hypospadias (urethral opening on the ventral surface of the penis) or incomplete fusion of the urogenital or labioscrotal folds. Females with pseudohermaphroditism are genetic females with virilized external genitalia, including clitoral hypertrophy and some degree of fusion of the urogenital or labioscrotal folds. Both types of pseudohermaphroditism are caused either by abnormal levels of sex hormones or abnormalities in the sex hormone receptors.

Another major category of genital tract abnormalities involves various types of uterovaginal malformations (Fig. 5.13), which occur in 0.16% of women (13). These malformations are believed to result from one or more of the following situations:





- Improper fusion of the paramesonephric ducts
- Incomplete development of one paramesonephric duct
- Failure of part of the paramesonephric duct on one or both sides to develop

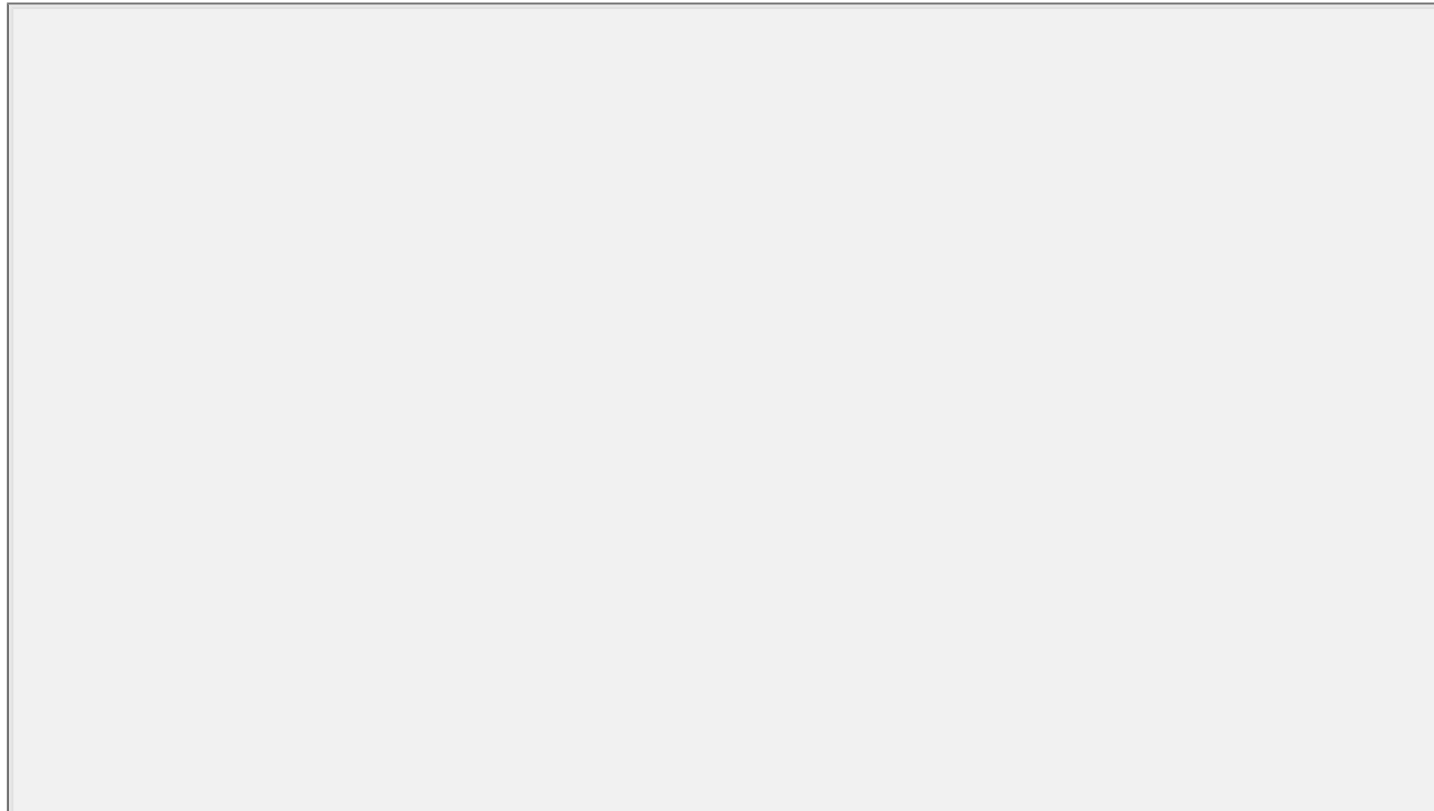
Absent or incomplete canalization of the vaginal plate

Genital Structures

Vagina

A sagittal section of the female pelvis is presented in Fig. 5.14.

The vagina is a hollow fibromuscular tube extending from the vulvar vestibule to the uterus. In the dorsal lithotomy position, the vagina is directed posteriorly toward the sacrum, but its axis is almost horizontal in the upright position. It is attached at its upper end to the uterus just above the cervix. The spaces between the cervix and vagina are known as the *anterior, posterior, and lateral vaginal fornices*. **Because the vagina is attached at a higher point posteriorly than anteriorly, the posterior vaginal wall is about 3 cm longer than the anterior wall.**



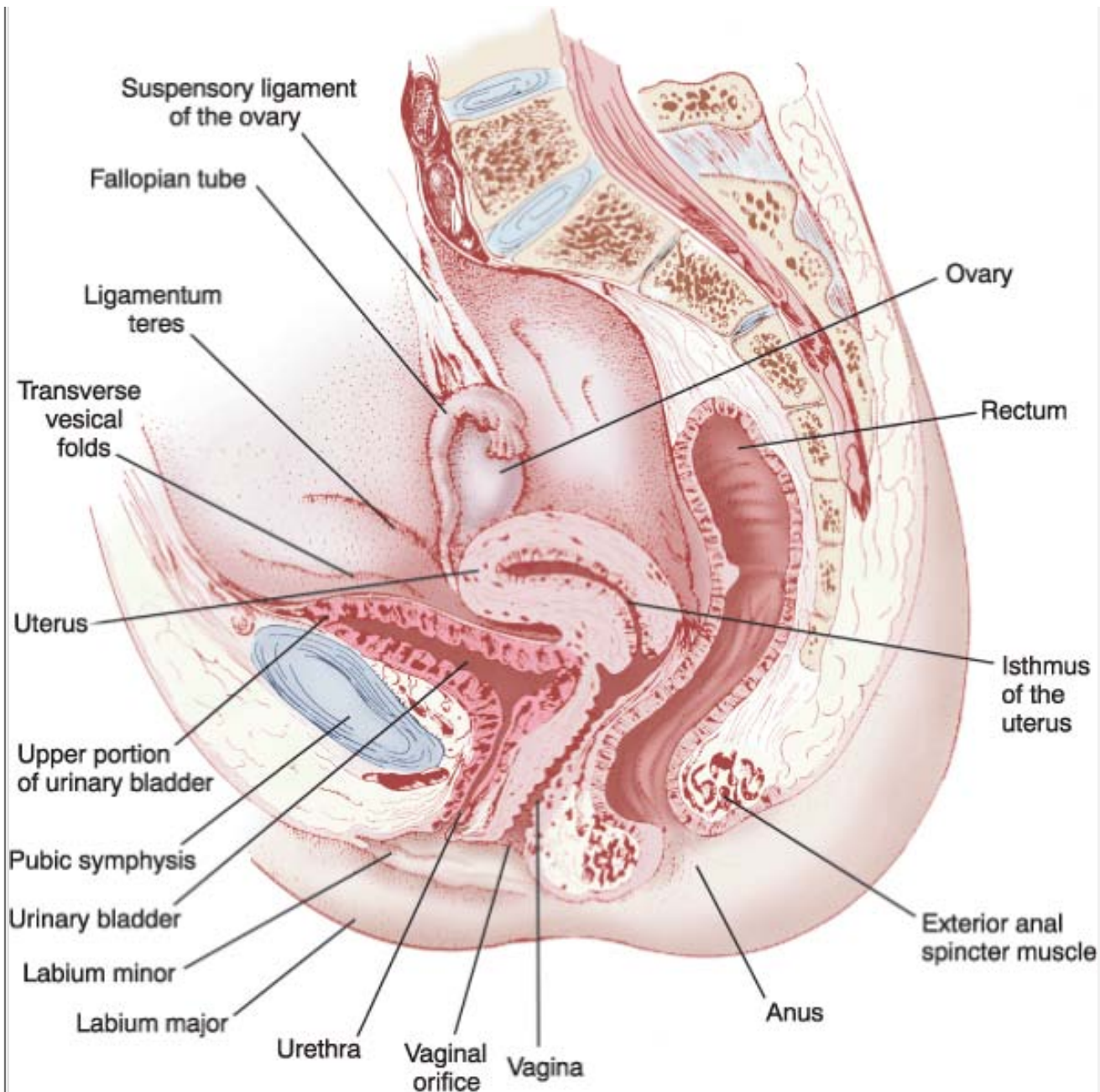


Figure 5.14 The pelvic viscera. A sagittal section of the female pelvis with the pelvic viscera and their relationships.

The posterior vaginal fornix is separated from the posterior cul-de-sac and peritoneal cavity by the vaginal wall and peritoneum. This proximity is clinically useful, both diagnostically and therapeutically. *Culdocentesis*, a technique in which a needle is inserted just posterior to the cervix through the vaginal wall into the peritoneal cavity, has been used to evaluate intraperitoneal hemorrhage (e.g., ruptured ectopic pregnancy, hemorrhagic corpus luteum, other intraabdominal bleeding), pus (e.g., pelvic inflammatory disease, ruptured intraabdominal abscess), or other intraabdominal fluid (e.g., ascites). Incision into the peritoneal cavity from this location in the vagina, known as a *posterior colpotomy*, can be used as an adjunct to laparoscopic excision of adnexal masses, with removal of the mass intact through the posterior vagina.

The vagina is attached to the lateral pelvic wall with endopelvic fascial connections to the *arcus tendineus (white line)*, which extends from the pubic bone to the ischial spine. This connection converts the vaginal lumen into a transverse slit with the anterior and posterior walls in apposition; the lateral space where the two walls meet is the vaginal sulcus. Lateral detachments of the vagina are recognized in some cystocele formation.

The opening of the vagina may be covered by a membrane or surrounded by a fold of connective tissue called the *hymen*. This tissue is usually replaced by irregular tissue tags later in life as sexual activity and childbirth occur. The lower vagina is somewhat constricted as it passes through the urogenital hiatus in the pelvic diaphragm; the upper vagina is more spacious. However, the entire vagina is characterized by its distensibility, which is most evident during childbirth.

The vagina is closely applied anteriorly to the urethra, bladder neck and trigonal region, and posterior bladder; posteriorly, the vagina lies in association with the perineal body, anal canal, lower rectum, and posterior cul-de-sac. **It is separated from both the lower urinary and gastrointestinal tracts by their investing layers of fibromuscular elements known as the *endopelvic fascia*.**

The vagina is composed of three layers:

- **Mucosa**—nonkeratinized stratified squamous epithelium, without glands. Vaginal lubrication occurs primarily by transudation, with contributions from cervical and Bartholin gland secretions. The mucosa has a characteristic pattern of transverse ridges and furrows, known as *rugae*. It is hormonally sensitive, responding to stimulation by estrogen with proliferation and maturation.

The mucosa is colonized by mixed bacterial flora with lactobacillus predominant; normal pH is 3.5

to 4.5.

- **Muscularis**—connective tissue and smooth muscle, loosely arranged in inner circular and outer longitudinal layers.
- **Adventitia**—endopelvic fascia, adherent to the underlying muscularis.

Blood Supply

The blood supply of the vagina includes the vaginal artery and branches from the uterine, middle rectal, and internal pudendal arteries.

Innervation

The innervation of the vagina is as follows: the upper vagina—uterovaginal plexus; the distal vagina—pudendal nerve.

Uterus

The uterus is a fibromuscular organ usually divided into a lower cervix and an upper corpus or uterine body (Fig. 5.15).

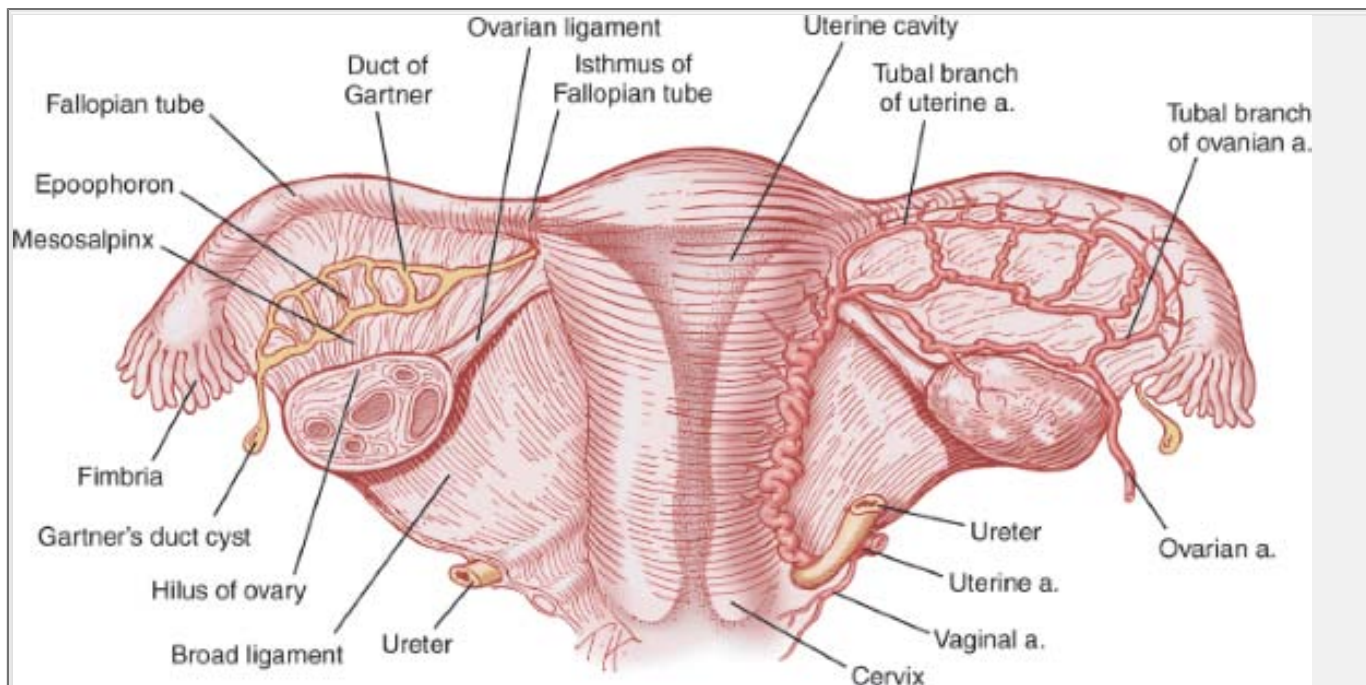


Figure 5.15 The uterus, fallopian tubes, and ovaries.

Cervix

The portion of cervix exposed to the vagina is the exocervix or portio vaginalis. It has a convex round surface with a circular or slitlike opening (the external os) into the endocervical canal. **The endocervical canal is about 2 to 3 cm in length and opens proximally into the endometrial cavity at the internal os.**

The cervical mucosa generally contains both stratified squamous epithelium, characteristic of the exocervix, and mucus-secreting columnar epithelium, characteristic of the endocervical canal. However, the intersection where these two epithelia meet—the squamocolumnar junction—is geographically variable and dependent on hormonal stimulation. It is this dynamic interface, the transformation zone, that is most vulnerable to the development of squamous neoplasia.

In early childhood, during pregnancy, or with oral contraceptive use, columnar epithelium may extend from the endocervical canal onto the exocervix, a condition known as *eversion* or *ectopy*. After menopause, the transformation zone usually recedes entirely into the endocervical canal.

Production of cervical mucus is under hormonal influence. It varies from profuse, clear, and thin mucus around the time of ovulation to scant and thick mucus in the postovulatory phase of the cycle. Deep in the mucosa and submucosa, the cervix is composed of fibrous connective tissue and a small amount of smooth muscle in a circular arrangement.

Corpus

The body of the uterus varies in size and shape, depending on hormonal and childbearing status.

At birth, the cervix and corpus are about equal in size; in adult women, the corpus has grown to 2 to 3 times the size of the cervix. The position of the uterus in relation to other pelvic structures is also variable and is generally described in terms of positioning— anterior, midposition, or posterior; flexion; and version. ***Flexion is the angle between the long axis of the uterine corpus and the cervix, whereas version is the angle of***

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the junction of the uterus with the upper vagina. Occasionally, abnormal positioning may occur secondary to associated pelvic pathology, such as endometriosis or adhesions.

The uterine corpus is divided into several different regions. The area where the endocervical canal opens into the endometrial cavity is known as the *isthmus or lower uterine segment*. On each side of the upper uterine body, a funnel-shaped area receives the insertion of the fallopian tubes and is called the *uterine cornu*; the uterus above this area is the fundus.

The endometrial cavity is triangular in shape and represents the mucosal surface of the uterine corpus. The epithelium is columnar and gland forming with a specialized stroma. It undergoes cyclic structural and functional change during the reproductive years, with regular shedding of the superficial endometrium and regeneration from the basal layer.

The muscular layer of the uterus, the myometrium, consists of interlacing smooth muscle fibers and ranges in thickness from 1.5 to 2.5 cm. Some outer fibers are continuous with those of the tube and round ligament.

Peritoneum covers most of the corpus of the uterus and the posterior cervix and is known as the *serosa*. Laterally, the broad ligament, a double layer of peritoneum covering the neurovascular supply to the uterus, inserts into the cervix and corpus. Anteriorly, the bladder lies over the isthmic and cervical region of the uterus.

Blood Supply

The blood supply to the uterus is the uterine artery, which anastomoses with the ovarian and vaginal arteries.

Innervation

The nerve supply to the uterus is the uterovaginal plexus.

Fallopian Tubes

The fallopian tubes and ovaries collectively are referred to as the *adnexa*. The fallopian tubes are paired hollow structures representing the proximal unfused ends of the müllerian duct. They vary in length from 7 to 12 cm, and their function includes ovum pickup, provision of physical environment for conception, and transport and nourishment of the fertilized ovum.

The tubes are divided into several regions:

- **Interstitial**—narrowest portion of the tube, lies within the uterine wall and forms the tubal ostia at the endometrial cavity.
- **Isthmus**—narrow segment closest to the uterine wall.
- **Ampulla**—larger diameter segment lateral to the isthmus.
- **Fimbria (infundibulum)**—funnel-shaped abdominal ostia of the tubes, opening into the peritoneal cavity; this opening is fringed with numerous fingerlike projections that provide a wide surface for ovum pickup. The fimbria ovarica is a connection between the end of the tube and ovary, bringing the two closer.

The tubal mucosa is ciliated columnar epithelium, which becomes progressively more architecturally complex as the fimbriated end is approached. The muscularis consists of an

inner circular and outer longitudinal layer of smooth muscle. The tube is covered by peritoneum and, through its mesentery (mesosalpinx), which is situated dorsal to the round ligament, is connected to the upper margin of the broad ligament.

Blood Supply

The vascular supply to the fallopian tubes is the uterine and ovarian arteries.

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Innervation

The innervation to the fallopian tubes is the uterovaginal plexus and the ovarian plexus.

Ovaries

The ovaries are paired gonadal structures that lie suspended between the pelvic wall and the uterus by the infundibulopelvic ligament laterally and the uteroovarian ligament medially.

Inferiorly, the hilar surface of each ovary is attached to the broad ligament by its mesentery (mesovarium), which is dorsal to the mesosalpinx and fallopian tube.

Primary neurovascular structures reach the ovary through the infundibulopelvic ligament and enter through the mesovarium. **The normal ovary varies in size, with measurements up to 5 × 3 × 3 cm.** Variation in dimension results from endogenous hormonal production, which varies with age and with each menstrual cycle. Exogenous substances, including oral contraceptives, gonadotropin-releasing hormone agonists, or ovulation-inducing medication, may either stimulate or suppress ovarian activity and, therefore, affect size.

Each ovary consists of a cortex and medulla and is covered by a single layer of flattened cuboidal to low columnar epithelium that is continuous with the peritoneum at the mesovarium. The cortex is composed of a specialized stroma and follicles in various stages of development or attrition. The medulla occupies a small portion of the ovary in its hilar region and is composed primarily of fibromuscular tissue and blood vessels.

Blood Supply

The blood supply to the ovary is the ovarian artery, which anastomoses with the uterine artery.

Innervation

The innervation to the ovary is the ovarian plexus and the uterovaginal plexus.

Urinary Tract

Ureters

The ureter is the urinary conduit leading from the kidney to the bladder; it measures about 25 cm in length and is totally retroperitoneal in location.

The lower half of each ureter traverses the pelvis after crossing the common iliac vessels at their bifurcation, just medial to the ovarian vessels. It descends into the pelvis adherent to the peritoneum of the lateral pelvic wall and the medial leaf of the broad ligament and enters the bladder base anterior to the upper vagina, traveling obliquely through the bladder wall to terminate in the bladder trigone.

The ureteral mucosa is a transitional epithelium. The muscularis consists of an inner longitudinal and outer circular layer of smooth muscle. A protective connective tissue sheath, which is adherent to the peritoneum, encloses the ureter.

Blood Supply

The blood supply is variable, with contributions from the renal, ovarian, common iliac, internal iliac, uterine, and vesical arteries.

Innervation

The innervation is through the ovarian plexus and the vesical plexus.

Bladder and Urethra

Bladder

The bladder is a hollow organ, spherically shaped when full, that stores urine. Its size varies with urine volume, normally reaching a maximum volume of at least 300

mL. The bladder is often divided into two areas, which are of physiologic significance:

- The **base of the bladder** consists of the urinary trigone posteriorly and a thickened area of detrusor anteriorly. The three corners of the trigone are formed by the two ureteral orifices and the opening of the urethra into the bladder. The bladder base receives α -adrenergic sympathetic innervation and is the area responsible for maintaining continence.
- The **dome of the bladder** is the remaining bladder area above the bladder base. It has parasympathetic innervation and is responsible for micturition.

The bladder is positioned posterior to the pubis and lower abdominal wall and anterior to the cervix, upper vagina, and part of the cardinal ligament. Laterally, it is bounded by the pelvic diaphragm and obturator internus muscle.

The bladder mucosa is transitional cell epithelium and the muscle wall (detrusor). Rather than being arranged in layers, it is composed of intermeshing muscle fibers.

Blood Supply

The blood supply to the bladder is from the superior, middle, and inferior vesical arteries, with contribution from the uterine and vaginal vessels.

Innervation

The innervation to the bladder is from the vesical plexus, with contribution from the uterovaginal plexus.

Urethra

The vesical neck is the region of the bladder that receives and incorporates the urethral lumen. The female urethra is about 3 to 4 cm in length and extends from the bladder to the vestibule, traveling just anterior to the vagina.

The urethra is lined by nonkeratinized squamous epithelium that is responsive to estrogen stimulation. Within the submucosa on the dorsal surface of the urethra are the paraurethral or Skene glands, which empty through ducts into the urethral lumen. Distally, these glands empty into the vestibule on either side of the external urethral orifice. Chronic infection of Skene glands, with obstruction of their ducts and cystic dilation, is believed to be an inciting factor in the development of suburethral diverticula.

The urethra contains an inner longitudinal layer of smooth muscle and outer, circularly oriented smooth muscle fibers. The inferior fascia of the urogenital diaphragm or perineal membrane begins at the junction of the middle and distal thirds of the urethra. Proximal to the middle and distal parts of the urethra, voluntary muscle fibers derived from the urogenital diaphragm intermix with the outer layer of smooth muscle, increasing urethral resistance and contributing to continence. At the level of the urogenital diaphragm, the skeletal muscle fibers leave the wall of the urethra to form the sphincter urethrae and deep transverse perineal muscles.

Blood Supply

The vascular supply to the urethra is from the vesical and vaginal arteries and the internal pudendal branches.

Innervation

The innervation to the urethra is from the vesical plexus and the pudendal nerve.

The lower urinary and genital tracts are intimately connected anatomically and functionally. In the midline, the bladder and proximal urethra can be dissected easily from the underlying lower uterine segment, cervix, and vagina through a loose avascular plane. The distal urethra is essentially inseparable from the vagina. Of surgical significance is the location of the bladder trigone immediately over the middle third of the vagina. Unrecognized injury to the bladder during pelvic surgery may result in development of a vesicovaginal fistula.

Fortunately, dissection to the level of the trigone is rarely required, and damage to this critical area is unusual. If dissection is carried too far laterally away from the midline, attachments between the bladder and cervix or vagina become much more dense and vascularized, resulting in increased blood loss and technical difficulty.

Lower Gastrointestinal Tract

Sigmoid Colon

The sigmoid colon begins its characteristic **S-shaped curve as it enters the pelvis at the left pelvic brim** (Fig. 5.16). The columnar mucosa and richly vascularized submucosa are surrounded by an inner circular layer of smooth muscle and three overlying longitudinal bands of muscle called tenia coli. A mesentery of varying length attaches the sigmoid to the posterior abdominal wall.

Blood Supply

The blood supply to the sigmoid colon is from the sigmoid arteries.

Innervation

The nerves to the sigmoid colon are derived from the inferior mesenteric plexus.

Rectum

The sigmoid colon loses its mesentery in the midsacral region and becomes the **rectum about 15 to 20 cm above the anal opening**. The rectum follows the curve of the lower sacrum and coccyx and becomes entirely retroperitoneal at the level of the rectouterine pouch or posterior cul-de-sac. It continues along the pelvic curve just posterior to the vagina until the level of the anal hiatus of the pelvic diaphragm, at which point it takes a sharp 90-degree turn posteriorly and becomes the anal canal, separated from the vagina by the perineal body.

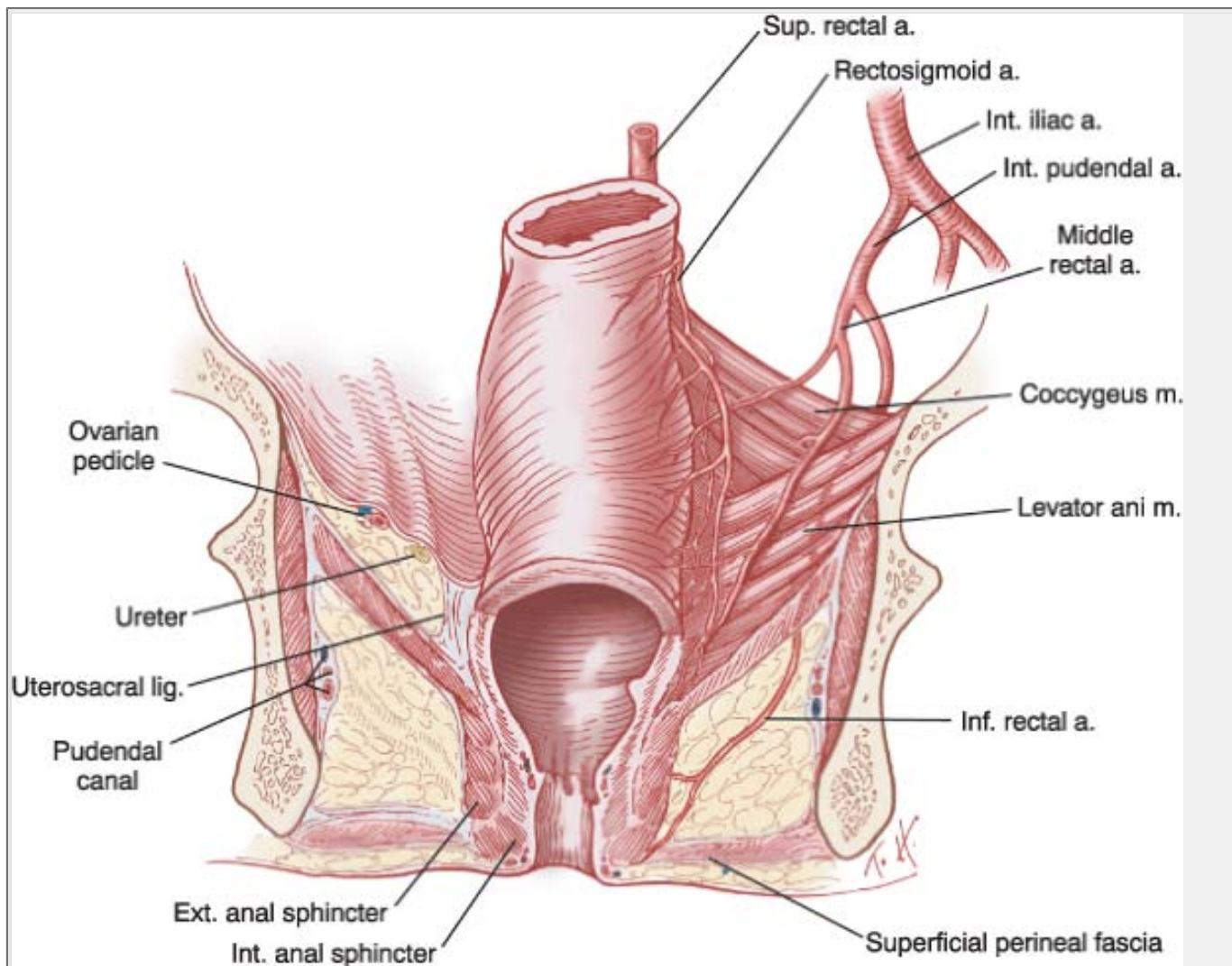


Figure 5.16 The rectosigmoid colon, its vascular supply, and muscular support.
 (Coronal view: peritoneum removed on right.)

The rectal mucosa is lined by a columnar epithelium and characterized by three transverse folds that contain mucosa, submucosa, and the inner circular layer of smooth muscle. The tenia of the sigmoid wall broaden and fuse over the rectum to form a continuous longitudinal external layer of smooth muscle to the level of the anal canal.

Anal Canal

The anal canal begins at the level of the sharp turn in the direction of the distal colon and is 2 to 3 cm in length. At the anorectal junction, the mucosa changes to stratified squamous epithelium (the pectinate line), which continues until the termination of the anus at the anal verge, where there is a transition to perianal skin with typical skin appendages. It is surrounded by a thickened ring of circular muscle fibers that is a continuation of the circular muscle of the rectum, the internal anal sphincter. Its lower part is surrounded by bundles of striated muscle fibers, the external anal sphincter (14).

Fecal continence is primarily provided by the puborectalis muscle and the internal and external anal sphincters. The puborectalis surrounds the anal hiatus in the pelvic diaphragm and interdigitates posterior to the rectum to form a rectal sling. The external anal sphincter surrounds the terminal anal canal below the level of the levator ani.

The anatomic proximity of the lower gastrointestinal tract to the lower genital tract is particularly important during surgery of the vulva and vagina. Lack of attention to this proximity during repair of vaginal lacerations or episiotomies can lead to damage of the rectum and resulting fistula formation or injury to the external anal sphincter resulting in fecal incontinence. Because of the avascular nature of the rectovaginal space, it is relatively easy to dissect the rectum from the vagina in the midline, which is routinely done in the repair of rectoceles.

Blood Supply

The vascular supply to the rectum and anal canal is from the superior, middle, and inferior rectal arteries. The venous drainage is a complex submucosal plexus of vessels that, under conditions of increased intraabdominal pressure (pregnancy, pelvic mass, ascites), may dilate and become symptomatic with rectal bleeding or pain as hemorrhoids.

Innervation

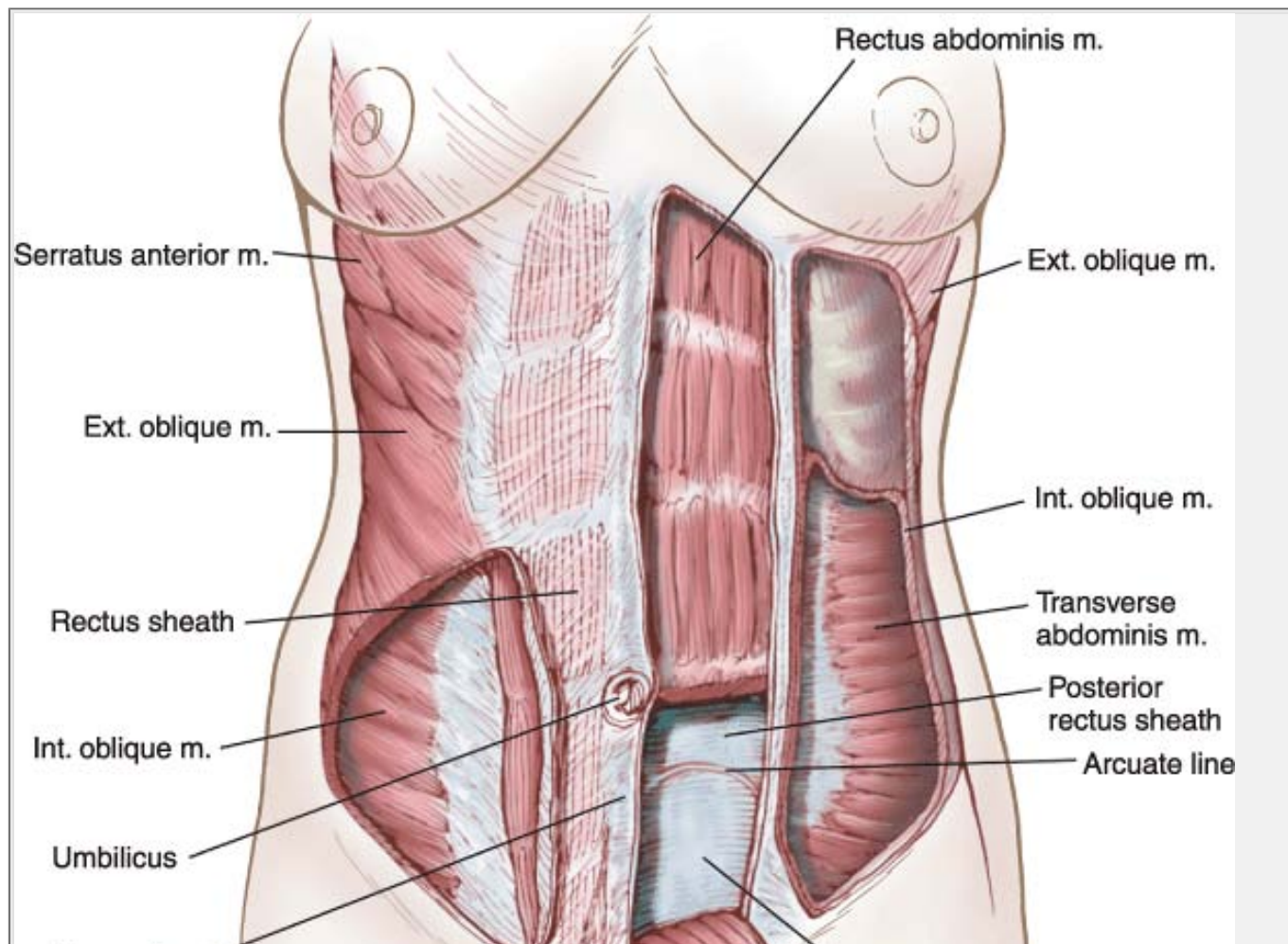
The nerve supply to the anal canal is from the middle rectal plexus, the inferior mesenteric plexus, and the pudendal nerve.

The Genital Tract and Its Relations

The genital tract is situated at the bottom of the intraabdominal cavity and is related to the intraperitoneal cavity and its contents, the retroperitoneal spaces, and the pelvic floor. Its access through the abdominal wall or the perineum requires a thorough knowledge of the anatomy of these areas and their relationships.

The Abdominal Wall

The anterior abdominal wall is bound superiorly by the xiphoid process and the costal cartilage of the seventh to tenth ribs and inferiorly by the iliac crest, anterosuperior iliac spine, inguinal ligament, and pubic bone. It consists of skin, muscle, fascia, and nerves and vessels.



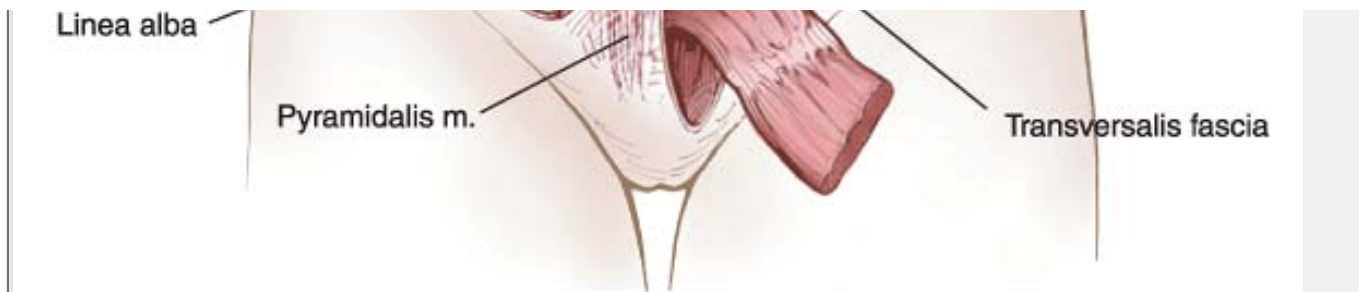


Figure 5.17 The abdominal wall muscles.

Skin

The lower abdominal skin may exhibit striae, or “stretch marks,” and increased pigmentation in the midline in parous women. The subcutaneous tissue contains a variable amount of fat.

Muscles

Five muscles and their aponeuroses contribute to the structure and strength of the anterolateral abdominal wall (Fig. 5.17; Table 5.7).

Fascia

Superficial Fascia

The superficial fascia consists of two layers:

- **Camper fascia**—the most superficial layer, which contains a variable amount of fat and is continuous with the superficial fatty layer of the perineum
- **Scarpa fascia**—a deeper membranous layer continuous in the perineum with Colles fascia (superficial perineal fascia) and with the deep fascia of the thigh (fascia lata).

Rectus Sheath

The aponeuroses of the external and internal oblique and the transversus abdominis combine to form a sheath for the rectus abdominis and pyramidalis, fusing medially in the midline at the linea alba and laterally at the semilunar line (Fig. 5.18). Above the arcuate line, the aponeurosis of the internal oblique muscle splits into anterior and posterior lamella (Fig. 5.18A). Below this line, all three layers are anterior to the body of the rectus muscle (Fig. 5.18B). The rectus is then covered posteriorly by the transversalis fascia, providing access to the muscle for the inferior epigastric vessels.

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Table 5.7 Muscles Contributing to the Structure and Strength of the Anterolateral Abdominal Wall

<i>Muscle</i>	<i>Origin</i>	<i>Insertion</i>	<i>Action</i>
External oblique	Fleshy digitations from the outer surfaces of ribs 5–12	Fibers radiate inferiorly, anteriorly, and medially, in most cases ending in the aponeurosis of the external muscle and inserting into the anterior half of the iliac crest, the pubic tubercle, and the linea alba. The superficial inguinal ring is located above and lateral to the pubic tubercle at the end of a triangular cleft in the external oblique muscle, bordered by strong fibrous bands that transmit the round ligament	Compresses and supports abdominal viscera; flexes and rotates vertebral column

Internal oblique	Posterior layer of the thoracolumbar fascia, the anterior two thirds of the iliac crest, and the lateral two thirds of the inguinal ligament	Inferior border of ribs 10–12. The superior fibers of the aponeurosis split to enclose the rectus abdominis muscle and join at the linea alba above the arcuate line. The most inferior fibers join with those of the transverse abdominis muscle to insert into the pubic crest and pecten pubis via the conjoint tendon	Compresses and supports abdominal viscera
Transversus abdominus	Inner aspect of the inferior six costal cartilages, the thoracolumbar fascia, the iliac crest, and the lateral one third of the inguinal ligament	Linea alba with the aponeurosis of the internal oblique, the pubic crest and the pecten pubis through the conjoint tendon	Compresses and supports abdominal viscera
Rectus abdominis	Superior pubic ramus and the ligaments of the symphysis pubis	Anterior surface of the xiphoid process and the cartilage of ribs 5–7	Tenses anterior abdominal wall and flexes trunk
Pyramidalis	Small triangular muscle contained within the rectus sheath, anterior to the lower part of the rectus muscle	On the linea alba, easily recognizable shape, used to locate the midline, particularly in a patient with previous abdominal surgery and scarring of the abdominal wall	Tenses the linea alba, insignificant in terms of function, and is frequently absent

Transversalis Fascia and Endopelvic Fascia

The transversalis fascia is a firm membranous sheet on the internal surface of the transversus abdominis muscle that extends beyond the muscle and forms a

fascia lining the entire abdominopelvic cavity. Like the peritoneum, it is divided into a parietal and a visceral component. It is continuous from side to side across the linea alba and covers the posterior aspect of the rectus abdominis muscle below the arcuate line. Superiorly, it becomes the inferior fascia of the diaphragm. Inferiorly, it is attached to the iliac crest, covers the iliac fascia and the obturator internus fascia, and extends downward and medially to form the superior fascia of the pelvic diaphragm.

Characteristically, the transversalis fascia continues along blood vessels and other structures leaving and entering the abdominopelvic cavity and contributes to the formation of the visceral (*endopelvic*) pelvic fascia (15). The pelvic fascia invests the pelvic organs and attaches them to the pelvic sidewalls, thereby playing a critical role in *pelvic support*. In the inguinal region, the fascial relationships result in the development of the inguinal canal, through which the round ligament exits into the perineum. The fascia is separated from the peritoneum by a layer of preperitoneal fat. Areas of fascial weaknesses or congenital or posttraumatic and surgical injuries result in herniation of the underlying structures through a defective abdominal wall. The incisions least likely to result in damage to the integrity and innervation of the abdominal wall muscles include a midline incision through the linea alba and a transverse incision through the recti muscle fibers that respects the integrity of its innervation (16).

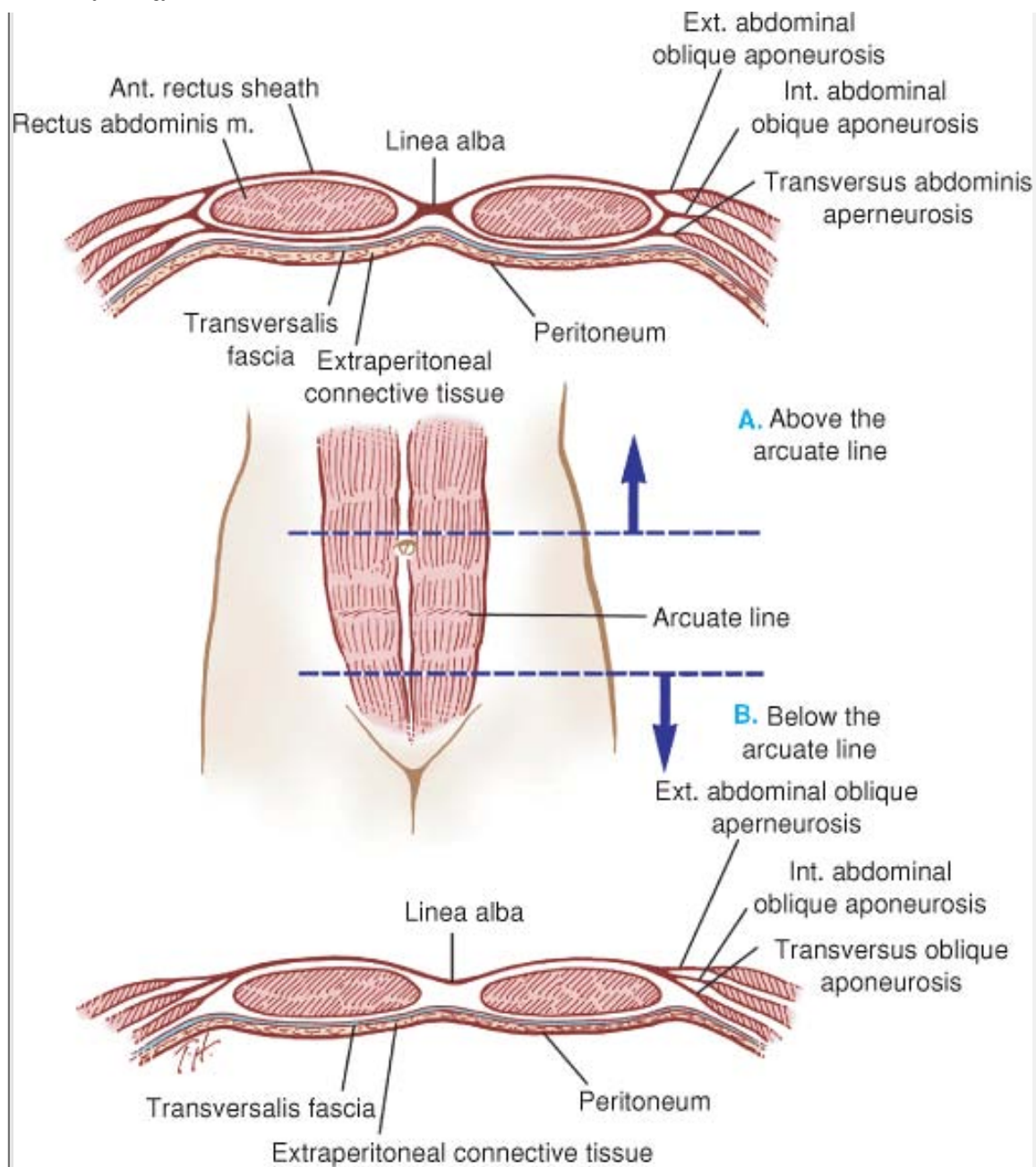


Figure 5.18 A transverse section of the rectus abdominis. The aponeurosis of the external and internal oblique and the transversus abdominis from the rectus abdominis. **A:** Above the arcuate line. **B:** Below the arcuate line.

Nerves and Vessels

The tissues of the abdominal wall are innervated by the continuation of the inferior intercostal nerves T4 to T11 and the subcostal nerve T12. The inferior part of the abdominal wall is supplied by the first lumbar nerve through the iliohypogastric and the ilioinguinal nerves. The primary blood supply to the anterior lateral abdominal wall includes the following:

- The **inferior epigastric and deep circumflex iliac arteries**, branches of the external iliac artery
- The **superior epigastric artery**, a terminal branch of the internal thoracic artery

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The inferior epigastric artery runs superiorly in the transverse fascia to reach the arcuate line, where it enters the rectus sheath. It is vulnerable to damage by abdominal incisions in which the rectus muscle is completely or partially transected or by excessive lateral traction on the rectus. The deep circumflex artery runs on the deep aspect of the anterior abdominal wall parallel to the inguinal ligament and along the iliac crest between the transverse abdominis muscle and the internal oblique muscle. The superior epigastric vessels enter the rectus sheath superiorly just below the seventh costal cartilage.

The venous system drains into the saphenous vein, and the lymphatics drain to the axillary chain above the umbilicus and to the inguinal nodes below it. The subcutaneous tissues drain to the lumbar chain.

Perineum

The perineum is situated at the lower end of the trunk between the buttocks. Its bony boundaries include the lower margin of the pubic symphysis anteriorly, the tip of the coccyx posteriorly, and the ischial tuberosities laterally. These landmarks correspond to the boundaries of the pelvic outlet. The diamond shape of the perineum is customarily divided by an imaginary line joining the ischial tuberosities immediately in front of the anus, at the level of the perineal body, into an anterior urogenital and a posterior anal triangle (Fig. 5.19).

Urogenital Triangle

The urogenital triangle includes the external genital structures and the urethral opening (Fig. 5.19). These external structures cover the superficial and deep perineal compartments (Figs. 5.20 and 5.21) and are known as the *vulva*.

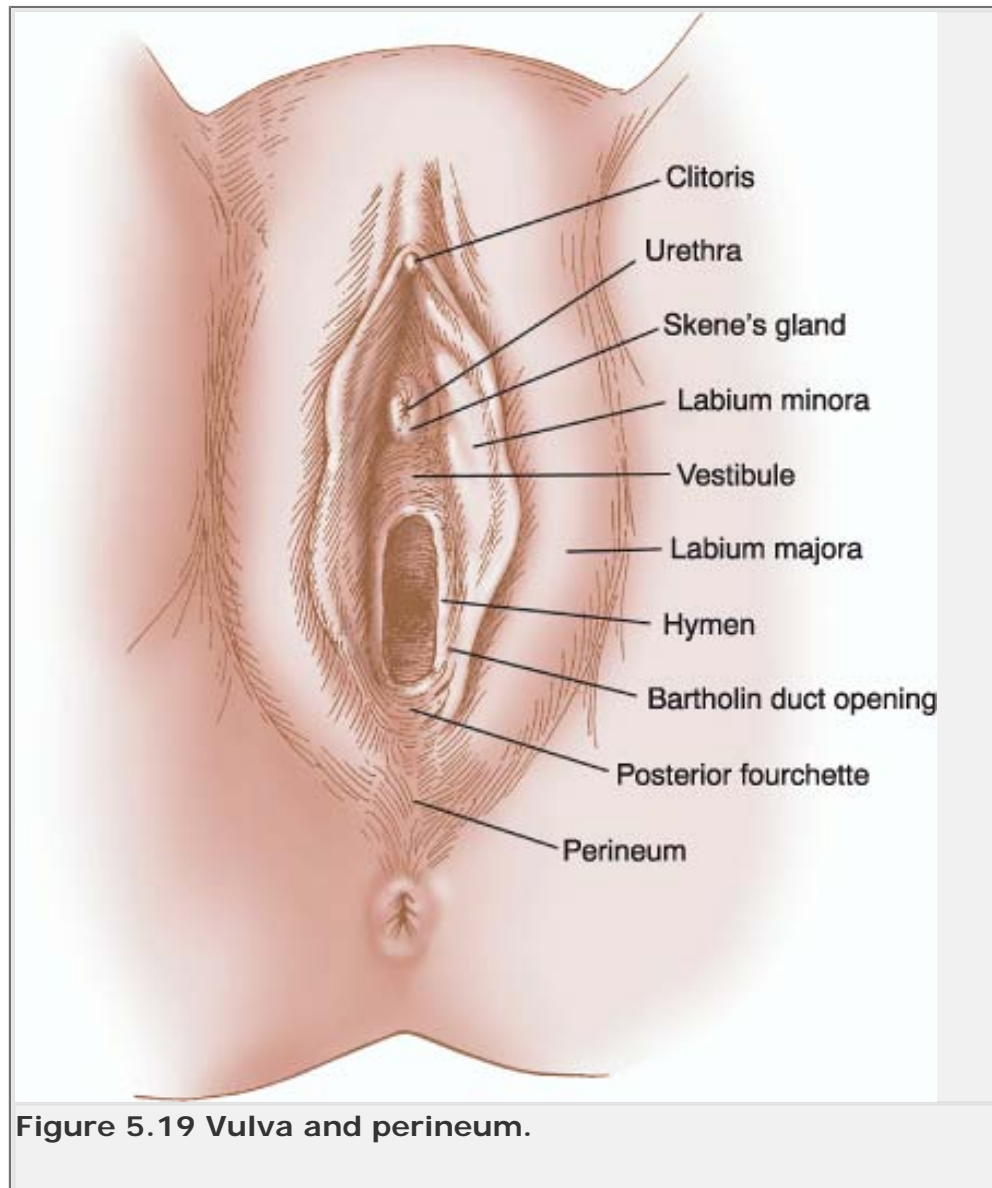


Figure 5.19 Vulva and perineum.

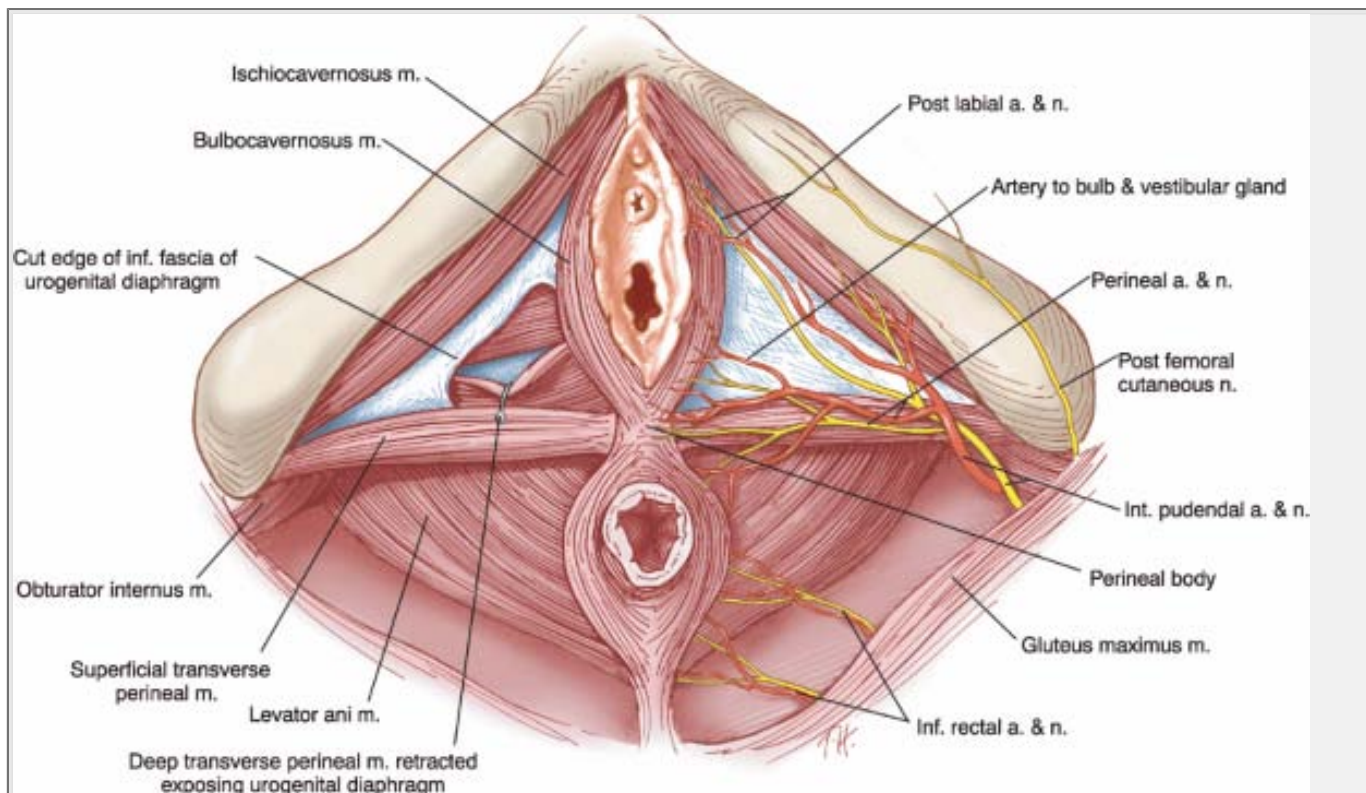


Figure 5.20 Superficial perineal compartment.

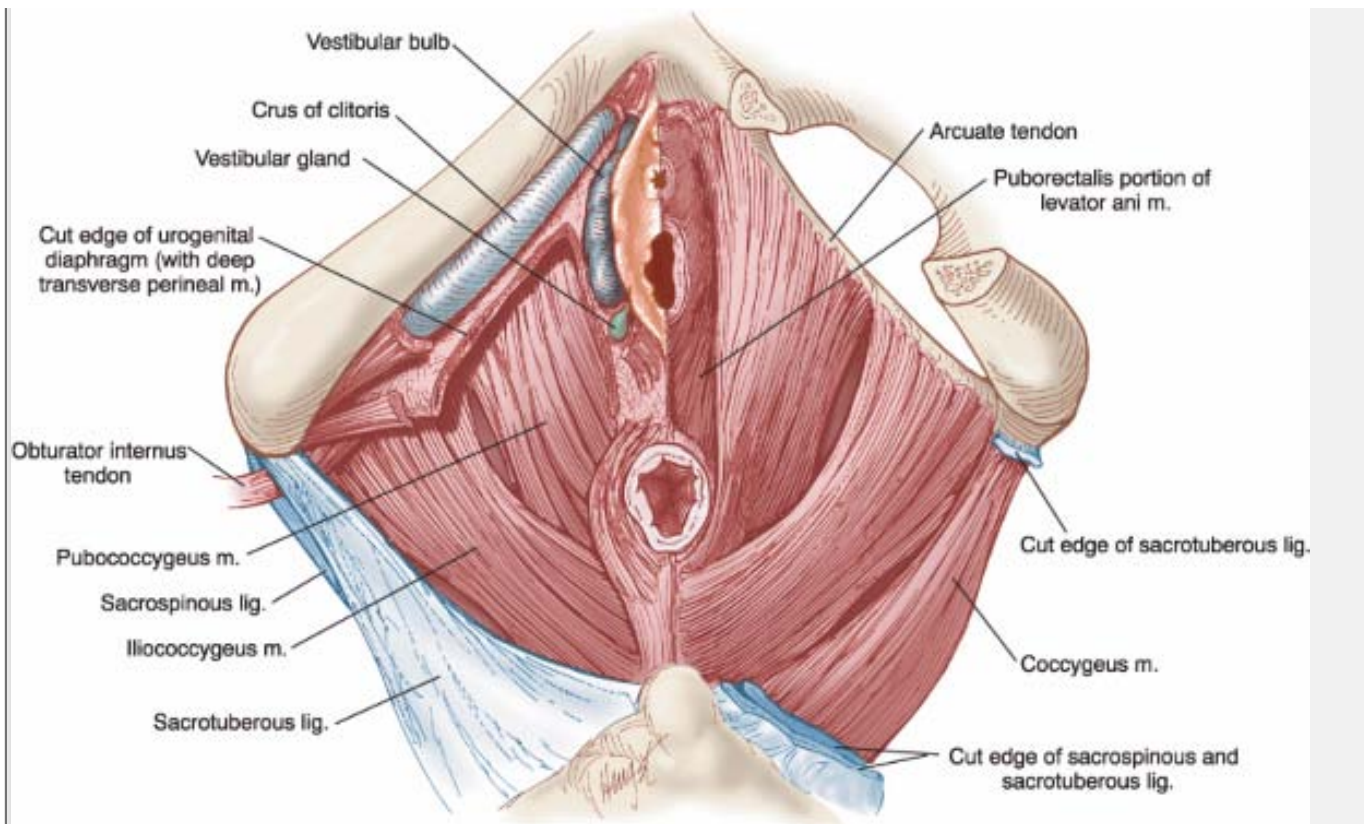


Figure 5.21 Deep perineal compartment.

Vulva

Mons Pubis

The mons pubis is a triangular eminence in front of the pubic bones that consists of adipose tissue covered by hair-bearing skin up to its junction with the abdominal wall.

Labia Majora

The labia majora are a pair of fibroadipose folds of skin that extend from the mons pubis downward and backward to meet in the midline in front of the anus at the

posterior fourchette. They include the terminal extension of the round ligament and occasionally a peritoneal diverticulum, the *canal of Nuck*. They are covered by skin with scattered hairs laterally and are rich in sebaceous, apocrine, and eccrine glands.

Labia Minora

The labia minora lie between the labia majora, with which they merge posteriorly, and are separated into two folds as they approach the clitoris anteriorly. The anterior folds unite to form the prepuce or hood of the clitoris. The posterior folds form the frenulum of the clitoris as they attach to its inferior surface. The labia minora are covered by hairless skin overlying a fibroelastic stroma rich in neural and vascular elements. The area between the posterior labia minora forms the vestibule of the vagina.

Clitoris

The clitoris is an erectile organ that is 2 to 3 cm in length. It consists of two crura and two corpora cavernosa and is covered by a sensitive rounded tubercle (the glans).

Vaginal Orifice

The vaginal orifice is surrounded by the *hymen*, a variable crescentic mucous membrane that is replaced by rounded caruncles after its rupture. The opening of the duct of the *greater vestibular (Bartholin) glands* is located on each side of the vestibule. Numerous lesser vestibular glands are also scattered posteriorly and between the urethral and vaginal orifices.

Urethral Orifice

The urethral orifice is immediately anterior to the vaginal orifice about 2 to 3 cm beneath the clitoris. The *Skene (paraurethral) gland* duct presents an opening on its posterior surface.

Superficial Perineal Compartment

The superficial perineal compartment lies between the superficial perineal fascia and the inferior fascia of the urogenital diaphragm (perineal membrane) (Fig. 5.20).

The superficial perineal fascia has a superficial and deep component. **The superficial layer is relatively thin and fatty and is continuous superiorly with the superficial fatty layer of the lower abdominal wall (*Camper fascia*).** It continues laterally as the fatty layer of the thighs. The deep layer of the superficial perineal (*Colles*) fascia is continuous superiorly with the deep layer of the superficial abdominal fascia (*Scarpa fascia*), which attaches firmly to the ischiopubic rami and ischial tuberosities. **The superficial perineal compartment is continuous superiorly with the superficial fascial spaces of the anterior abdominal wall, allowing spread of blood or infection along that route.** Such spread is limited laterally by the ischiopubic rami, anteriorly by the transverse ligament of

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the perineum, and posteriorly by the superficial transverse perineal muscle. The superficial perineal compartment includes the following.

Erectile Bodies

The vestibular bulbs are 3-cm, highly vascular structures surrounding the vestibule and located under the bulbocavernosus muscle. The body of the clitoris is attached by two crura to the internal aspect of the ischiopubic rami. They are covered by the ischiocavernosus muscle.

Muscles

The muscles of the vulva are the ischiocavernosus, the bulbocavernosus, and superficial transverse perineal. They are included in the superficial perineal as follows:

Ischiocavernosus

- Origin—ischial tuberosity
- Insertion—ischiopubic bone
- Action—compresses the crura and lowers the clitoris

Bulbocavernosus

- Origin—perineal body
- Insertion—posterior aspect of the clitoris; some fibers pass above the dorsal vein of the clitoris in a slinglike fashion
- Action—compresses the vestibular bulb and dorsal vein of the clitoris

Superficial Transverse Perineal

- Origin—ischial tuberosity
- Insertion—central perineal tendon
- Action—fixes the perineal body

Vestibular Glands

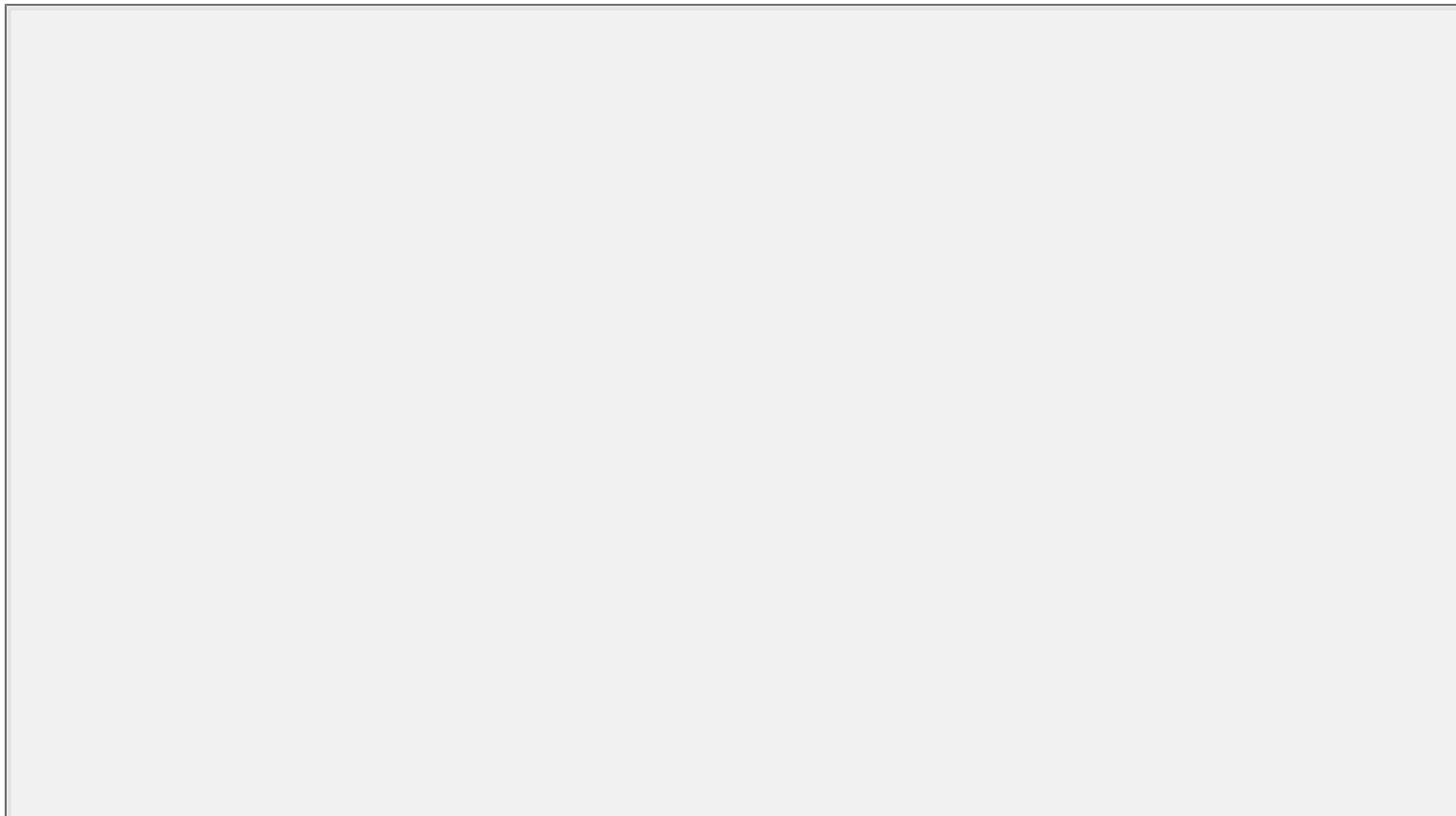
The vestibular glands are situated on either side of the vestibule under the posterior end of the vestibular bulb. They drain between the hymen and the labia minora. Their mucous secretion helps maintain adequate lubrication. Infection in these glands can result in an abscess.

Deep Perineal Compartment

The deep perineal compartment is a fascial space bound inferiorly by the

perineal membrane and superiorly by a deep fascial layer that separates the urogenital diaphragm from the anterior recess of the ischiorectal fossa (Fig. 5.21). It is stretched across the anterior half of the pelvic outlet between the ischiopubic rami. The deep compartment may be directly continuous with the pelvic cavity superiorly (17). Indeed, the posterior pubourethral ligaments, functioning as winglike elevations of the fascia ascending from the pelvic floor to the posterior aspect of the symphysis pubis, provide a point of fixation to the urethra and support the concept of the continuity of the deep perineal compartment with the pelvic cavity.

The anterior pubourethral ligaments represent a similar elevation of the inferior fascia of the urogenital diaphragm and are joined by the intermediate pubourethral ligament, with the junction between the two fascial structures arcing under the pubic symphysis (18). The urogenital diaphragm includes the *sphincter urethrae* (*urogenital sphincter*) and the *deep transverse perineal* (*transversus vaginae*) muscle.



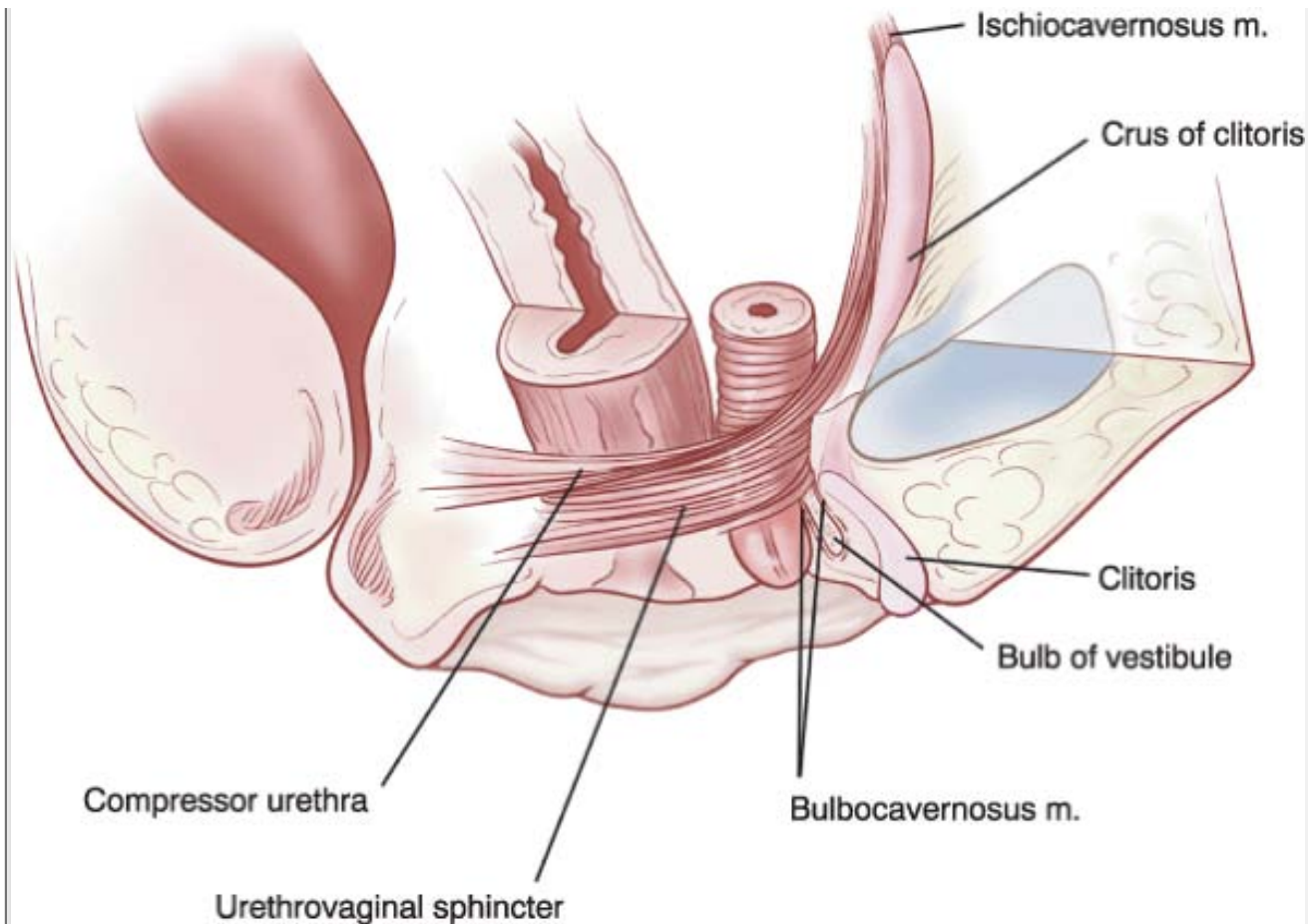


Figure 5.22 The complete urogenital sphincter musculature, bladder, and vagina. (Redrawn from **Haderer JM, Pannu HK, Genadry R, et al.** Controversies in female urethral anatomy and their significance for understanding urinary continence: observations and literature review. *Int Urogynecol J Pelvic Floor Dysfunct* 2002; 13(4): 236–252, with permission.)

The sphincter urethrae (Fig. 5.22) is a continuous muscle fanning out as it develops proximally and distally, including the following:

- The **external urethral sphincter**, which surrounds the middle third of the urethra
- The **compressor urethrae**, arcing across the ventral side of the urethra

The **urethrovaginal sphincter**, which surrounds the ventral aspect of the urethra and terminates in the lateral vaginal wall

The deep transverse perineal muscle originates at the internal aspect of the ischial bone, parallels the muscle compressor urethrae, and attaches to the lateral vaginal wall along the perineal membrane.

The urinary and genital tracts have a common reliance on several interdependent structures for support. **The cardinal and uterosacral ligaments are condensations of endopelvic fascia that support the cervix and upper vagina over the levator plate.**

Laterally, endopelvic fascial condensations attach the midvagina to the pelvic walls at the arcus tendineus fascia pelvis anteriorly and the arcus tendineus levator ani posteriorly. The distal anterior vagina and urethra are anchored to the urogenital diaphragm, and the distal posterior vagina to the perineal body.

Anteriorly, the pubourethral ligaments and pubovesical fascia and ligaments provide fixation and stabilization for the urethra and bladder. Posteriorly, they rely on the vagina and lower uterus for support. Partial resection or relaxation of the uterosacral ligaments often leads to relaxation of the genitourinary complex, resulting in the formation of a cystocele. Various types and degrees of genital tract prolapse or relaxation are almost always associated with similar findings in the bladder, urethra, or both.

Blood Supply

The blood supply to the vulva is as follows:

- External pudendal artery (from femoral artery), internal pudendal artery
- Venous drainage—internal pudendal veins

The blood supply to the superficial and deep perineal compartments is as follows:

Internal pudendal artery, dorsal artery of the clitoris

- Venous drainage—internal pudendal veins, which are richly anastomotic
- Lymphatic drainage—internal iliac chain

Innervation

The innervation to the vulva is from branches of the following nerves:

- Ilioinguinal nerve
- Genitofemoral nerve (genital branch)
- Lateral femoral cutaneous nerve of the thigh (perineal branch)
- Perineal nerve (branch of pudendal)

Superficial and deep perineal compartments are innervated by the perineal nerve.

Perineal Body

The perineal body or central perineal tendon is critical to the posterior support of the lower aspect of the anterior vaginal wall. It is a triangle-shaped structure separating the distal portion of the anal and vaginal canals that is formed by the convergence of the tendinous attachments of the bulbocavernosus, the external anal sphincter, and the superficial transverse perinei muscle. Its superior border represents the point of insertion of the *rectovaginal (Denonvilliers) fascia*, which extends to the underside of the peritoneum covering the cul-de-sac of Douglas, separating the anorectal from the urogenital compartment (19). The perineal body also plays an important anchoring role in the musculofascial support of

The perineal body represents the central connection between the two layers of support of the pelvic floor—the pelvic and urogenital diaphragm. It also provides a posterior connection to the anococcygeal raphe. Thus, it is central to the definition of the bilevel support of the floor of the pelvis.

Anal Triangle

The anal triangle includes the lower end of the anal canal. The external anal sphincter surrounds the anal triangle, and the ischiorectal fossa is on each side. Posteriorly, the *anococcygeal body* lies between the anus and the tip of the coccyx and consists of thick fibromuscular tissue (of levator ani and external anal sphincter origin) giving support to the lower part of the rectum and the anal canal.

The external anal sphincter forms a thick band of muscular fibers arranged in three layers running from the perineal body to the anococcygeal ligament. The subcutaneous fibers are thin and surround the anus and, without bony attachment, decussate in front of it. The superficial fibers sweep forward from the anococcygeal ligament, and the tip of the coccyx around the anus inserts into the perineal body. The deep fibers arise from the perineal body to encircle the lower half of the anal canal to form a true sphincter muscle, which fuses with the puborectalis portion of the levator ani.

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The ischiorectal fossa is mainly occupied by fat and separates the ischium laterally from the median structures of the anal triangle. It is a fascia-lined space located between the perineal skin inferiorly and the pelvic diaphragm superiorly; it communicates with the contralateral ischiorectal fossa over the anococcygeal ligament. Superiorly, its apex is at the origin of the levator ani muscle from the obturator fascia. It is bound medially by the levator ani and the external sphincter with their fascial covering, laterally by the obturator internus muscle with its fascia, posteriorly by the sacrotuberous ligament and the lower border of the gluteus maximus muscle, and anteriorly by the base of the urogenital diaphragm. It is widest and deepest posteriorly and weakest medially.

An ischiorectal abscess should be drained without delay, or it will extend into the anal canal. The cavity is filled with fat that cushions the anal canal and is traversed by many fibrous bands, vessels, and nerves, including the pudendal and the inferior rectal nerves. The perforating branch of S2 and S3 and the perineal branch of S4 also run through this space.

The *pudendal (Alcock) canal* is a tunnel formed by a splitting of the inferior portion of the

obturator fascia running anteromedially from the ischial spine to the posterior edge of the urogenital diaphragm. It contains the pudendal artery, vein, and nerve in their traverse from the *pelvic* cavity to the perineum.

Blood Supply

The blood supply to the anal triangle is from the inferior rectal (hemorrhoidal) artery and vein.

Innervation

The innervation to the anal triangle is from the perineal branch of the fourth sacral nerve and the inferior rectal (hemorrhoidal) nerve.

Retroperitoneum and Retroperitoneal Spaces

The subperitoneal area of the true pelvis is partitioned into potential spaces by the various organs and their respective fascial coverings and by the selective thickenings of the endopelvic fascia into ligaments and septa (Fig. 5.23). It is imperative that surgeons operating in the pelvis be familiar with these spaces, as discussed below.

Prevesical Space

The prevesical (Retzius) space is a fat-filled potential space bound anteriorly by the pubic bone, covered by the transversalis fascia, and extending to the umbilicus between the medial umbilical ligaments (obliterated umbilical arteries); posteriorly, the space extends to the anterior wall of the bladder. It is separated from the paravesical space by the ascending bladder septum (bladder pillars).

Upon entering the prevesical space, the pubourethral ligaments may be seen inserting the posterior aspect of the symphysis pubis as a thickened prolongation of the arcus tendineus fascia. With combined abdominal and vaginal bladder neck suspensory procedures, the point of entry is usually the Retzius space between the arcus tendineus and the pubourethral ligaments.

Paravesical Space

The paravesical spaces are fat filled and limited by the fascia of the obturator internus muscle and the pelvic diaphragm laterally, the bladder pillar medially, the endopelvic fascia inferiorly, and the lateral umbilical ligament superiorly.

Vesicovaginal Space

The vesicovaginal space is separated from the Retzius space by the endopelvic fascia. This space is limited anteriorly by the bladder wall (from the proximal urethra to the upper vagina), posteriorly by the anterior vaginal wall, and laterally by the bladder septa (selective thickenings of the endopelvic fascia inserting laterally into the arcus tendineus). **A tear in these fascial investments and thickenings medially, transversely, or laterally allows herniation and development of a cystocele.**

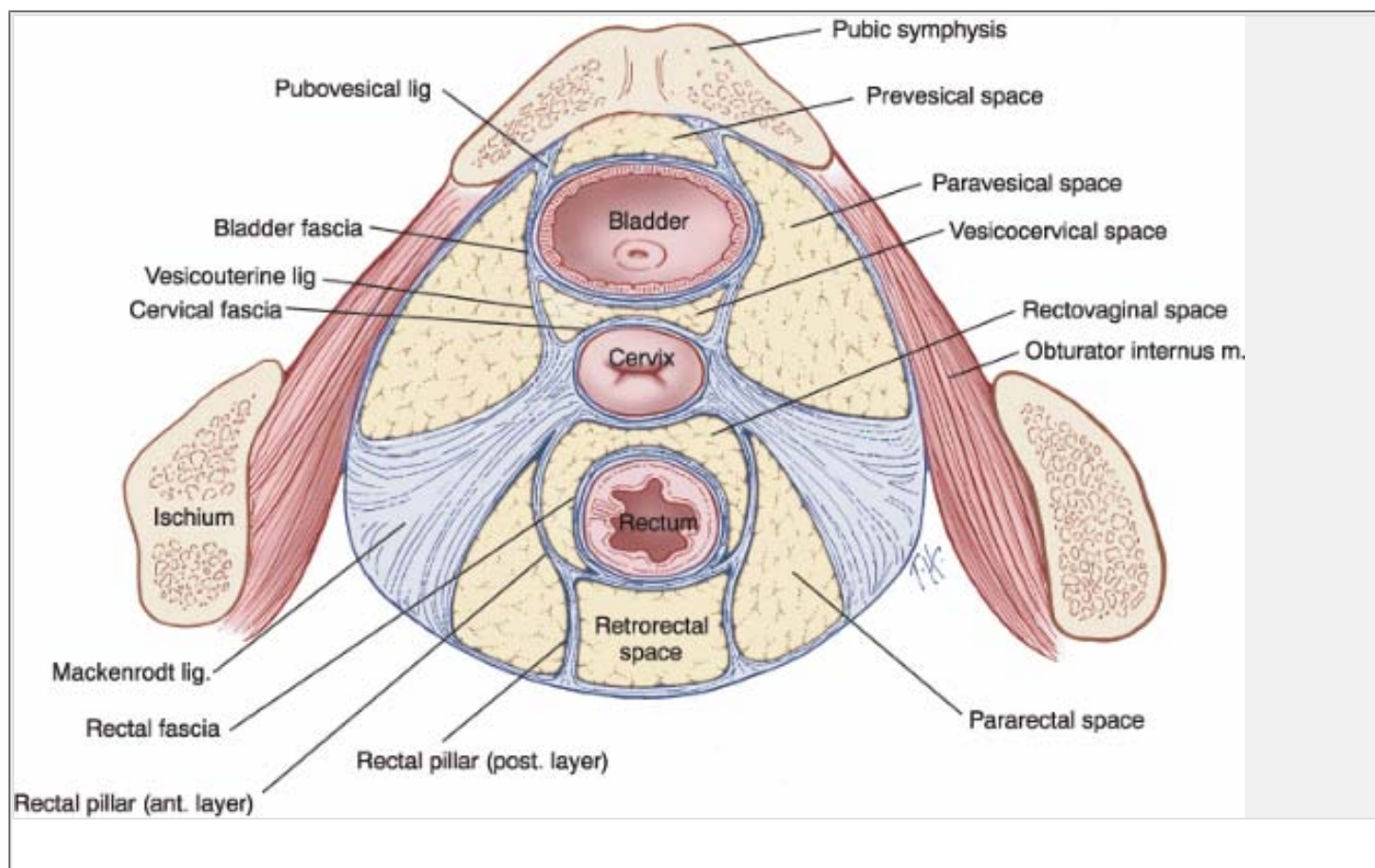


Figure 5.23 Schematic sectional drawing of the pelvis shows the firm connective tissue covering. The bladder, cervix, and rectum are surrounded by a connective tissue covering. The Mackenrodt ligament extends from the lateral cervix to the lateral abdominal pelvic wall. The vesicouterine ligament originating from the anterior edge of the Mackenrodt ligament leads to the covering of the bladder on the posterior side. The sagittal rectum column spreads both to the connective tissue of the rectum and the sacral vertebrae closely nestled against the back of the Mackenrodt ligament and lateral pelvic wall. Between the firm connective tissue bundles is loose connective tissue (paraspaces). (From **Von Peham H, Amreich JA.** *Gynaekologische Operationslehre*. Berlin, Germany: S Karger, 1930, with permission.)

Rectovaginal Space

The rectovaginal space extends between the vagina and the rectum from the superior border of the perineal body to the underside of the rectouterine Douglas pouch. It is bound anteriorly by the rectovaginal septum (firmly adherent to the posterior aspect of the vagina), posteriorly by the anterior rectal wall, and laterally by the descending rectal septa separating the rectovaginal space from the pararectal space on each side. The rectovaginal septum represents a firm membranous transverse septum dividing the pelvis into rectal and urogenital compartments, allowing the independent function of the vagina and rectum and providing support for the rectum. It is fixed laterally to the pelvic sidewall by rectovaginal fascia (part of the endopelvic fascia) along a line extending from the posterior fourchette to the arcus tendineus fasciae pelvis, midway between the pubis and the ischial spine (20). An anterior rectocele often results from a defective *septum* or an avulsion of the septum from the perineal body. Reconstruction of the perineum is critical for the restoration of this important compartmental separation as well as for the support of the anterior vaginal wall (21).

Lateral detachment of the rectovaginal fascia from the pelvic sidewall may constitute a "pararectal" defect analogous to anterior paravaginal defects.

Pararectal Space

The pararectal space is bound laterally by the levator ani, medially by the rectal pillars, and posteriorly above the ischial spine by the anterolateral aspect of the sacrum. It is separated from the retrorectal space by the posterior extension of the descending rectal septa.

Retrorectal Space

The retrorectal space is limited by the rectum anteriorly and the anterior aspect of the sacrum posteriorly. It communicates with the pararectal spaces laterally above the uterosacral ligaments and extends superiorly into the presacral space.

Presacral Space

The presacral space is the superior extension of the retrorectal space and is limited by the deep parietal peritoneum anteriorly and the anterior aspect of the sacrum posteriorly. It harbors the middle sacral vessels and the hypogastric plexi between the bifurcation of the aorta invested by loose areolar tissue. Presacral neurectomy requires familiarity with and working knowledge of this space.

Peritoneal Cavity

The female pelvic organs lie at the bottom of the abdominopelvic cavity covered superiorly and posteriorly by the small and large bowel. Anteriorly, the uterine wall is in contact with the posterosuperior aspect of the bladder. The uterus is held in position by the following structures:

- The **round ligaments** coursing inferolaterally toward the internal inguinal ring
- The **uterosacral ligaments**, which provide support to the cervix and upper vagina and interdigitate with fibers from the cardinal ligament near the cervix
- The **cardinal ligaments**, which provide support to the cervix and upper vagina and contribute to the support of the bladder

Anteriorly, the uterus is separated from the bladder by the vesicouterine pouch and from the rectum posteriorly by the rectouterine pouch or Douglas cul-de-sac. Laterally, the bilateral broad ligaments carry the neurovascular pedicles and their respective fascial coverings, attaching the uterus to the lateral pelvic sidewall.

The broad ligament is in contact inferiorly with the paravesical space, the obturator fossa, and the pelvic extension of the iliac fossa, to which it provides a peritoneal covering, and with the uterosacral ligament. Superiorly, it extends into the infundibulopelvic ligament.

Ureter

In its pelvic path, in the retroperitoneum, several relationships are of significance and identify areas of greatest vulnerability to injury of the ureter (Fig. 5.24):

- **The ovarian vessels cross over the ureter as it approaches the pelvic brim and lie in proximity just lateral to the ureter as it enters the pelvis.**
 - **As the ureter descends into the pelvis, it runs within the broad ligament just lateral to the uterosacral ligament, separating the uterosacral ligament from the mesosalpinx, mesovarium, and ovarian fossa.**
 - **At about the level of the ischial spine, the ureter crosses under the uterine artery in its course through the cardinal ligament; the ureter divides this area into the supraureteric parametrium surrounding the uterine vessels and the infraureteric paracervix molded around the vaginal vessels and extending posteriorly into the uterosacral ligament. In this location, the ureter lies 2 to 3 cm lateral to the cervix and in proximity to the insertion of the uterosacral ligament at the cervix. This proximity warrants caution when using the uterosacral ligament for vaginal vault suspension (22).**
-
- **The ureter then turns medially to cross the anterior upper vagina as it traverses the bladder wall.**

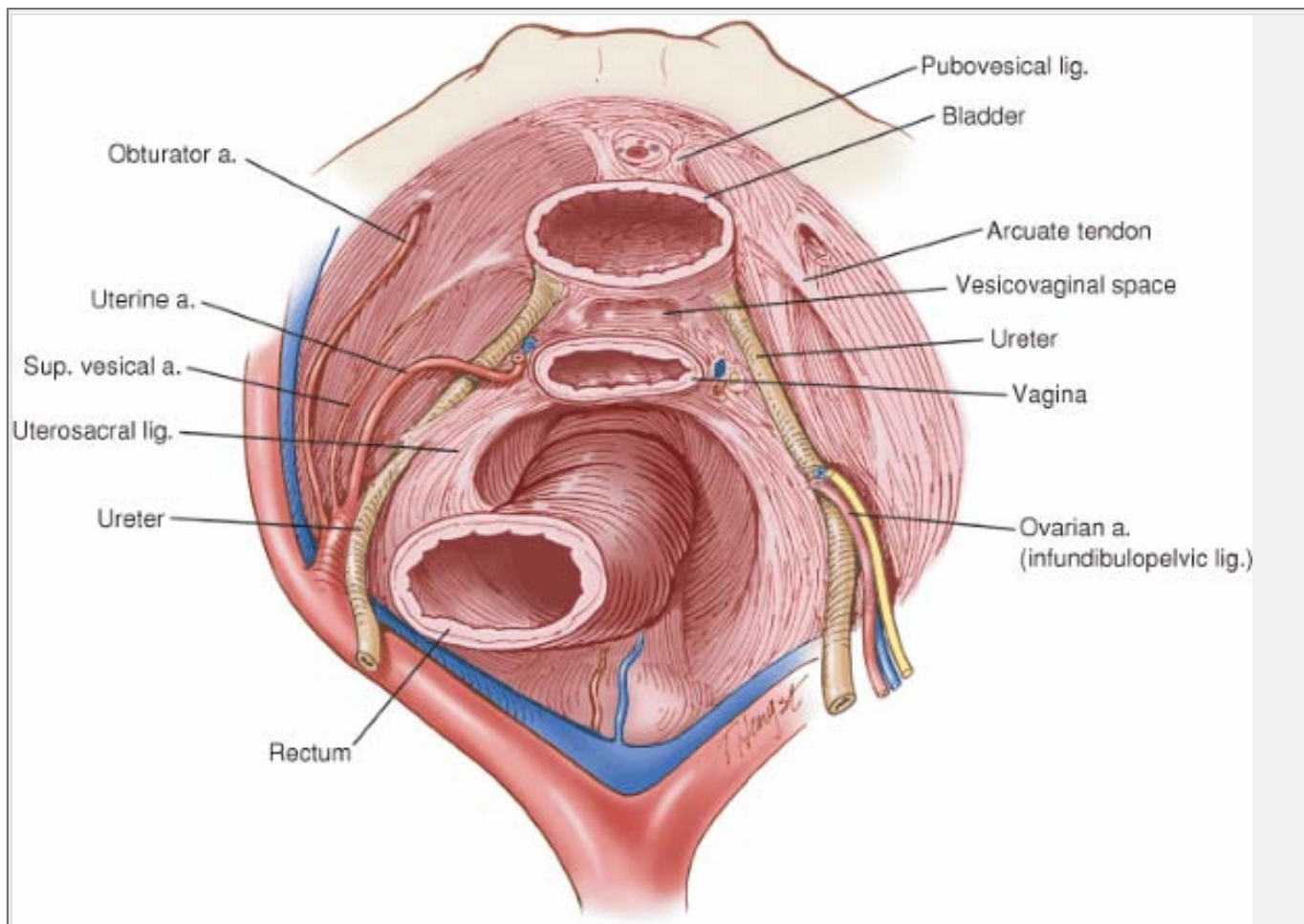


Figure 5.24 The course of the ureter and its relationship to the sites of greatest vulnerability.

About 75% of all iatrogenic injuries to the ureter result from gynecologic procedures, most commonly abdominal hysterectomy (23). Distortions of pelvic anatomy, including adnexal masses, endometriosis, other pelvic adhesive disease, or fibroids, may increase susceptibility to injury by displacement or alteration of usual anatomy.

Careful identification of the course of the ureter before securing the infundibulopelvic ligament and uterine artery is the best protection against ureteric injury during hysterectomy or adnexectomy. Even with severe intraperitoneal disease, however, the ureter can always be identified using a retroperitoneal approach and noting fundamental landmarks and relationships.

Pelvic Floor

The pelvic floor includes all of the structures closing the pelvic outlet from the skin inferiorly to the peritoneum superiorly. It is commonly divided by the pelvic diaphragm into a pelvic and a perineal portion (24). The pelvic diaphragm is spread transversely in a hammocklike fashion across the true pelvis, with a central hiatus for the urethra, vagina, and rectum. Anatomically and physiologically, the pelvic diaphragm can be divided into two components—the internal and external components.

The *external component* originates from the arcus tendineus, extending from the pubic bone to the ischial spine. It gives rise to fibers of differing directions, including the *pubococcygeus*, the *iliococcygeus*, and the *coccygeus*.

The *internal component* originates from the pubic bone above and medial to the origins of the pubococcygeus and is smaller but thicker and stronger (24). Its fibers run in a sagittal direction and are divided into the following two portions:

- *Pubovaginalis* fibers run in a perpendicular direction to the urethra, crossing the lateral vaginal wall at the junction of its lower one third and upper two thirds to insert into the perineal body. The intervening anterior interlevator space is covered by the urogenital diaphragm.
- *Puborectalis* superior fibers sling around the rectum to the symphysis pubis; its inferior fibers insert into the lateral rectal wall between the internal and external sphincter.

The pelvic diaphragm is covered superiorly by fascia, which includes a parietal and a visceral component and is a continuation of the transversalis fascia (Fig. 5.25). The parietal fascia has areas of thickening (ligaments, septae) that provide reinforcement and fixation for the pelvic floor. **The visceral (*endopelvic*) fascia extends medially to invest the pelvic viscera, resulting in a fascial covering to the bladder, vagina, uterus, and rectum. It becomes attenuated where the peritoneal covering is well defined and continues laterally with the pelvic cellular tissue and neurovascular pedicles.**

Musculofascial elements (the hypogastric sheath) extend along the vessels originating from

the internal iliac artery. Following these vessels to their respective organs, the hypogastric sheath extends perivascular investments that contribute to the formation of the endopelvic fascia so critical for the support of the pelvic organs.

Thus, the parietal fascia anchors the visceral fascia, which defines the relationship of the various viscera and provides them with significant fixation (uterosacral and cardinal ligaments), septation (vesicovaginal and rectovaginal), and definition of pelvic spaces (prevesical, vesicovaginal, rectovaginal, paravesical, pararectal, and retrorectal).

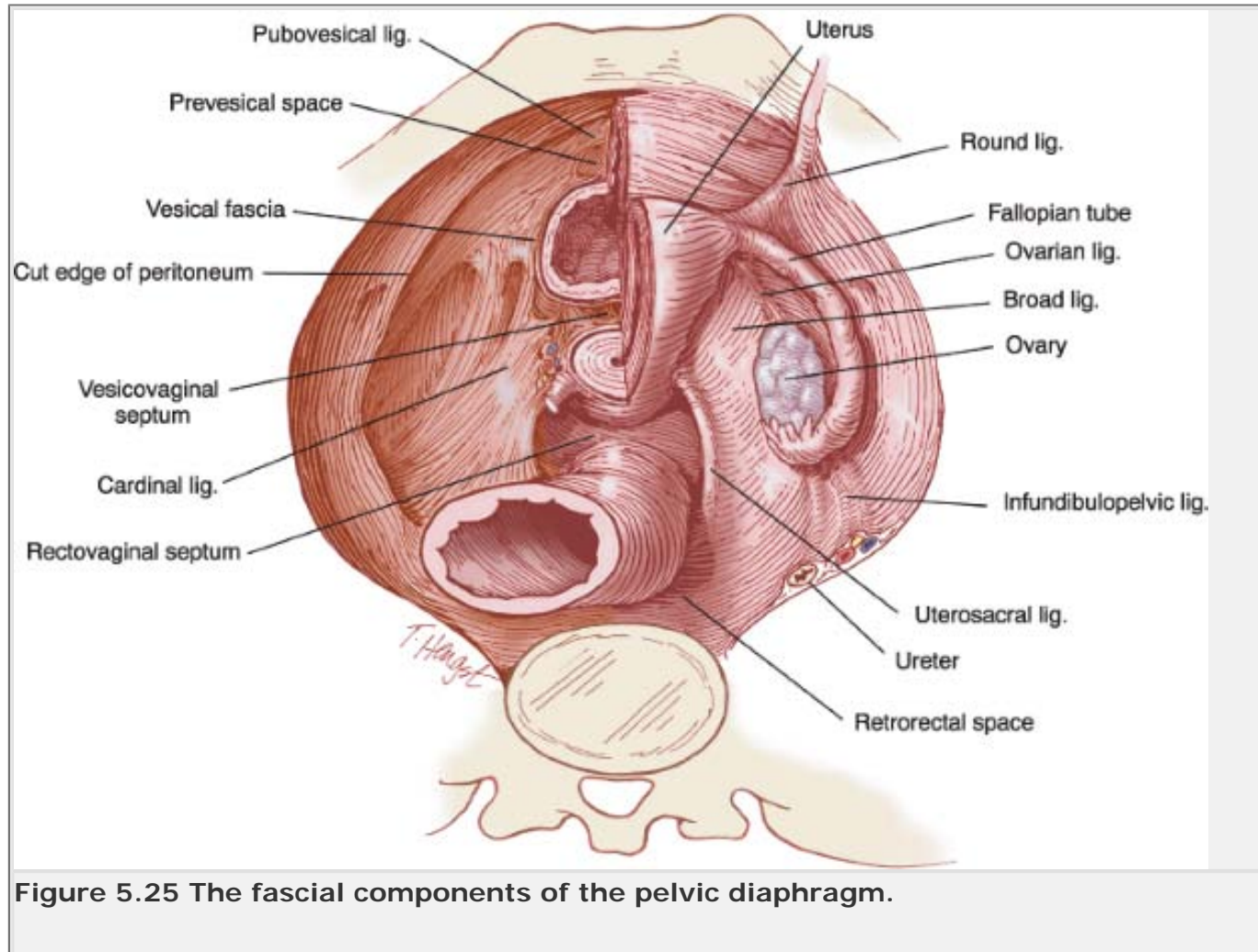


Figure 5.25 The fascial components of the pelvic diaphragm.

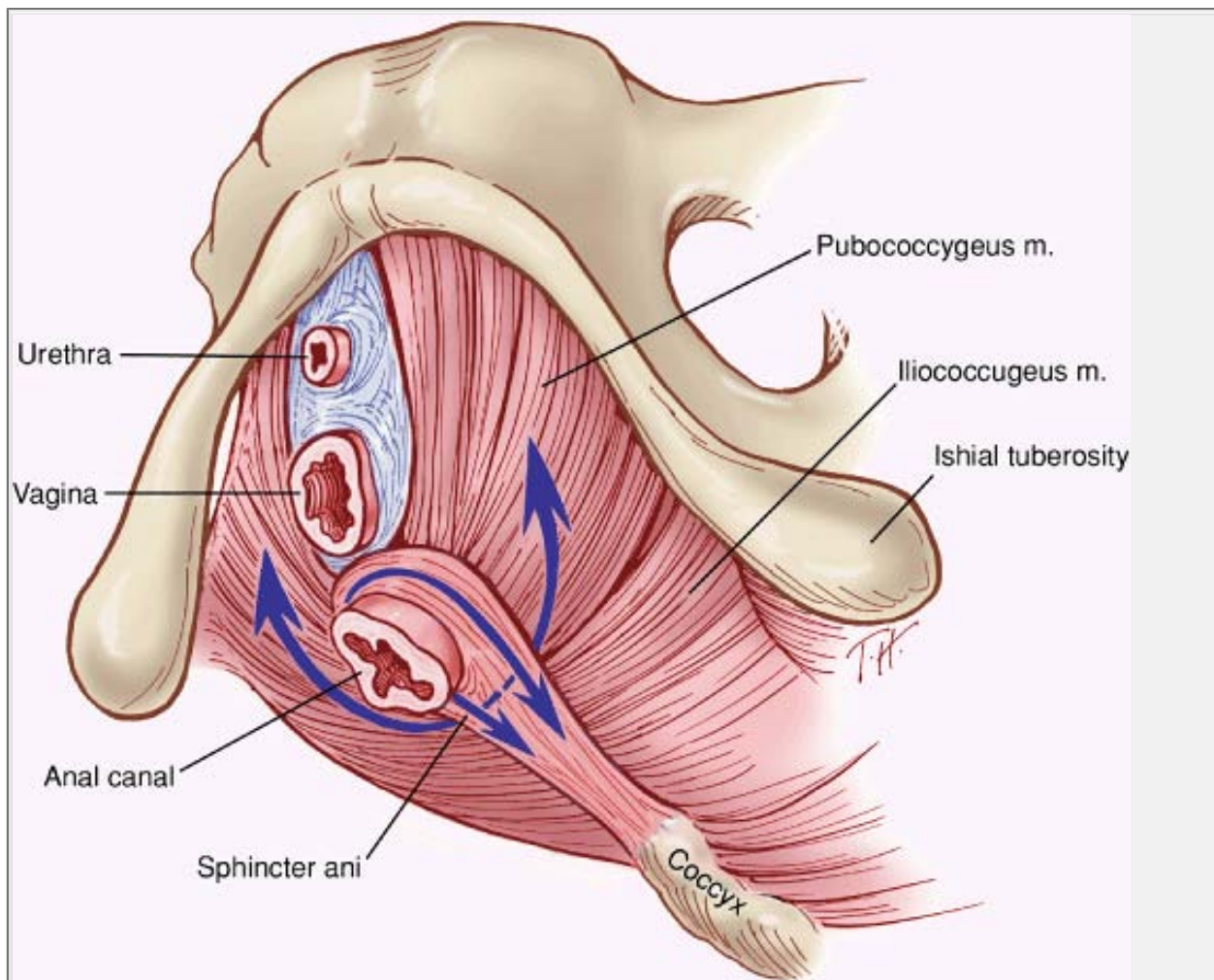


Figure 5.26 The double-layered muscular support of the pelvic diaphragm.

For its support, the pelvic floor relies on the complementary role of the pelvic diaphragm and its fascia resting on the perineal fibromuscular complex. It is composed of the perineal membrane (urogenital diaphragm) anteriorly, and the perineal body joined to the anococcygeal raphe by the external anal sphincter posteriorly. This double-layered arrangement, when intact, provides optimal support for the pelvic organs and counterbalances the forces pushing them downward with gravity and with any increase in intraabdominal pressure (Fig. 5.26). Dynamic imaging techniques, such as MRI, CT, and ultrasonography, are increasingly used to provide additional information in the evaluation of pelvic floor problems by visualizing anatomic landmarks during different functional phases.

Summary

New surgical approaches are being developed to solve old problems and often require surgeons to revisit familiar anatomy from an unfamiliar perspective (e.g., through a laparoscope) or with a different understanding of complex anatomic relationships. Anatomic alterations secondary to disease, congenital variation, or intraoperative complications may make even familiar surgical territory suddenly seem foreign. All of these situations require surgeons to be perpetual students of anatomy, regardless of their breadth or depth of experience.

Several strategies for continuing education in anatomy are suggested:

- **Review relevant anatomy before each surgical procedure.**
 - **Study the gynecologic literature on an ongoing basis—numerous publications have documented the evolution of newer concepts regarding anatomic issues such as pelvic support.**
-
- **Operate with more experienced pelvic surgeons, particularly when incorporating new surgical procedures into practice.**
 - **Periodically dissect fresh or fixed cadaveric specimens; this practice can generally be arranged through local or regional anatomy boards or medical schools or by special arrangement at the time of autopsy.**
 - **Take advantage of newer computer-generated 3D pelvic models and virtual reality interactive anatomic and surgical simulators, when available, to better understand functional anatomy and to help plan complicated surgical procedures (25,26).**

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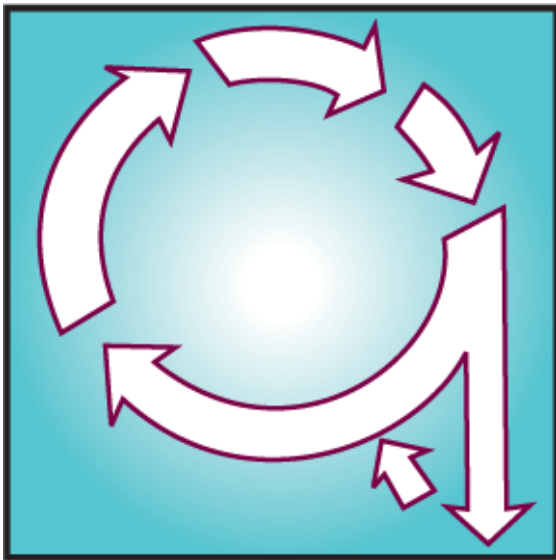
6

Molecular Biology and Genetics

Oliver Dorigo

Otoniel Martínez-Maza

Jonathan S. Berek



- The regulation and maintenance of normal tissue requires a balance between cell proliferation and programmed cell death, or *apoptosis*.
- The regulation of ovarian function occurs through *autocrine*, *paracrine*, and *endocrine* mechanisms. Disruption of these autocrine and paracrine intraovarian pathways may be the basis of polycystic ovarian disease, disorders of ovulation, and ovarian neoplastic disease.
- Among the genes that participate in control of cell growth and function, *proto-oncogenes* and *tumor suppressor genes* are particularly important.
- Growth factors trigger intracellular biochemical signals by binding to cell membrane receptors. In general, these membrane-bound receptors are *protein kinases* that convert an extracellular signal into an intracellular signal. Many of the proteins that participate in the intracellular signal transduction system are encoded by *proto-oncogenes* that are divided

into subgroups based on their cellular location or enzymatic function.

- **Oncogenes** comprise a family of genes that result from gain of function mutations of their normal counterparts, **proto-oncogenes**. The normal function of proto-oncogenes is to stimulate proliferation in a controlled context. Activation of oncogenes can lead to stimulation of cell proliferation and development of a malignant phenotype.

- **Tumor suppressor genes** are involved in the development of most cancers and are usually inactivated in a two-step process in which both copies of the tumor suppressor gene are mutated or inactivated by epigenetic mechanisms like methylation. The most commonly mutated tumor suppressor gene in human cancers is *p53*.

- **T lymphocytes** have a central role in the generation of immune responses by acting as helper cells in both humoral and cellular immune responses and by acting as effector cells in cellular responses. T cells can be distinguished from other types of lymphocytes by their cell surface phenotype, based on the

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pattern of expression of various molecules, as well as by differences in their biologic functions.

- There are two major subsets of mature T cells that are phenotypically and functionally distinct: *T helper/inducer cells*, which express the CD4 cell surface marker, and the *T suppressor/cytotoxic cells*, which express the CD8 marker. T_H1 and T_H2 are two helper T-cell subpopulations that control the nature of an immune response by secreting a characteristic and mutually antagonistic set of cytokines: Clones of T_H1 produce IL-2 and IFN- γ , whereas T_H2 clones produce IL-4, IL-5, IL-6, and IL-10.

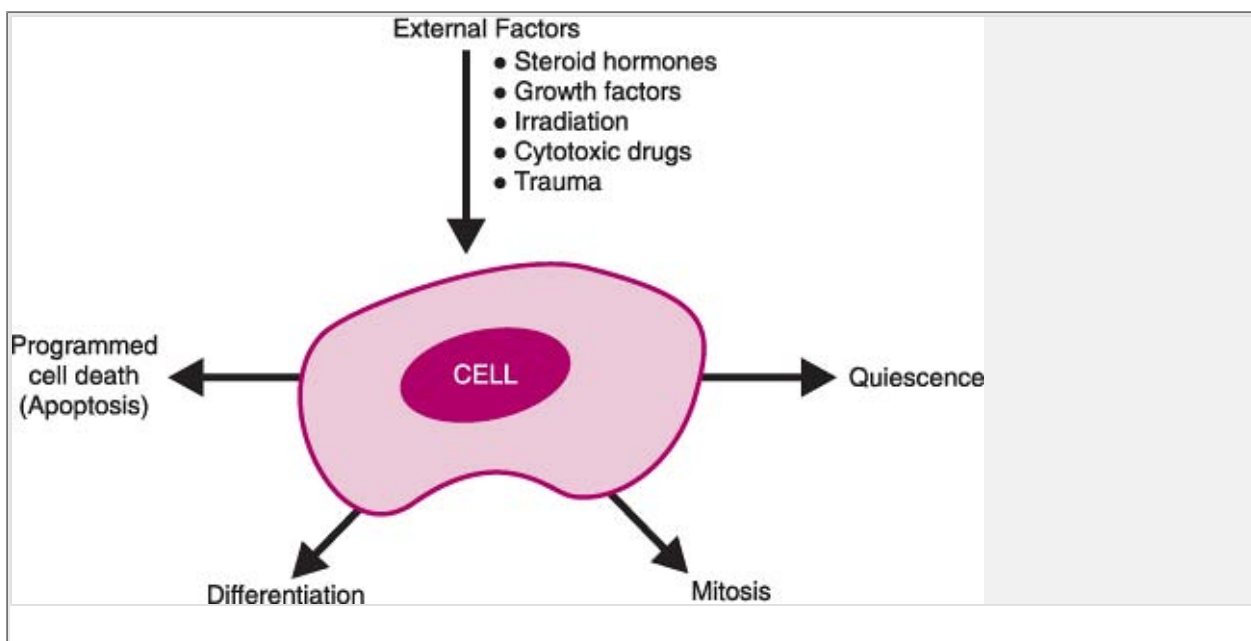


Figure 6.1 External stimuli affect the cell, which has a specific coordinated response.

Recent advances in molecular biology and genetics have led to improved understanding of basic biologic concepts and disease development. The knowledge acquired with the completion of the human genome project, the development of novel diagnostic modalities like microarray technology for the analysis of DNA and proteins, as well as the emergence of treatment strategies that target specific disease mechanisms, all have an increasing impact on the specialty of obstetrics and gynecology.

Normal cells are characterized by discrete metabolic, biochemical, and physiologic mechanisms. Specific cell types differ with respect to their mainly genetically determined responses to external influences (Fig. 6.1). In general, an external stimulus is converted to an intracellular signal, for example, via a cell membrane receptor. The intracellular signal is transferred to the nucleus and generates certain genetic responses that lead to changes in cellular function, differentiation, and proliferation. Although specific cell types and tissues exhibit unique functions and responses, many basic aspects of cell biology and genetics are common to all eukaryotic cells.

Cell Cycle

Normal Cell Cycle

Adult eukaryotic cells possess a well-balanced system of continuous production of DNA (transcription) and proteins (translation). Proteins are constantly degraded and replaced depending on the specific cellular requirements. Cells proceed through a sequence of phases called the cell cycle, during which the DNA is distributed to two daughter cells (*mitosis*) and subsequently duplicated (*synthesis phase*). This process is controlled at key checkpoints that monitor the status of a cell, for example, the amount of DNA present. The cell cycle is regulated by a small number of heterodimeric protein kinases that consist of a regulatory subunit (cyclin) and a catalytic subunit (cyclin-dependent kinase). Association of a cyclin with a cyclin-dependent kinase (CdkC) determines which proteins will be phosphorylated at a specific point during the cell cycle.

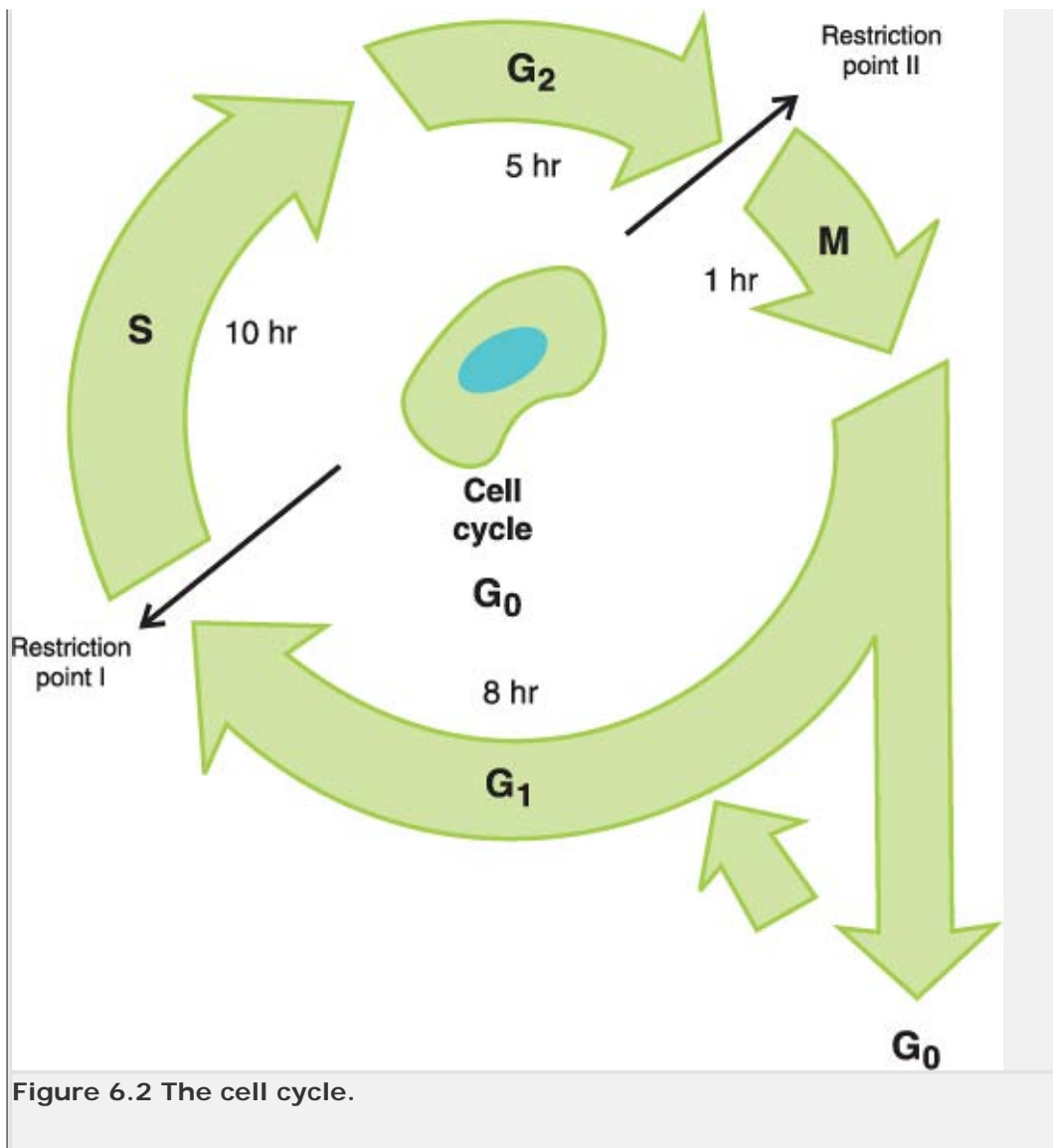


Figure 6.2 The cell cycle.

The cell cycle is divided into four major phases: M phase (mitosis), G₁ phase (period between mitosis and initiation of DNA replication), S phase (DNA synthesis), and G₂ phase (period between completion of DNA synthesis and mitosis) (Fig. 6.2). Postmitotic cells can "exit" the cell cycle into the so-called G₀ phase and remain for days, weeks, or even a lifetime without further proliferation. The duration of the cell cycle may be highly variable, although most human cells complete the cell cycle within approximately 24 hours. During a typical cell cycle, mitosis lasts about 30 to 60 minutes, the G₁ phase 7 to 10 hours, S phase 10 hours, and G₂ phase 5 hours. With respect to the cell cycle, there are three subpopulations of cells:

- **Terminally differentiated cells** cannot reenter the cell cycle.
- **Quiescent (G₀) cells** can enter the cell cycle if appropriately stimulated.
- **Dividing cells** are currently in the cell cycle.

Red blood cells, striated muscle cells, uterine smooth muscle cells, and nerve cells are terminally differentiated. Other cells, such as fibroblasts, exit from the G_1 phase into the G_0 phase and are considered to be out of the cell cycle. These cells enter the cell cycle following exposure to specific stimuli, such as growth factors and steroid hormones. Dividing cells are found in the gastrointestinal tract, the skin, and the cervix.

G₁ Phase

In response to specific external stimuli, cells enter the cell cycle by moving from the G_0 phase into the G_1 phase. The processes during G_1 phase lead to the synthesis of enzymes and regulatory proteins necessary for DNA synthesis during S phase, and are mainly regulated by G_1 cyclin-dependent kinase–cyclin complexes (G_1 CdkC). Complexes of G_1 CdkC induce degradation of the S phase inhibitors in late G_1 . Release of the S phase CdkC complex subsequently stimulates entry into the S phase. **Variations in the duration of the G_1 phase of the cell cycle, ranging from less than 8 hours to longer than 100 hours, account for the different generation times exhibited by different types of cells.**

S Phase

The nuclear DNA content of the cell is duplicated during the S phase of the cell cycle. The S phase CdkC complex activates proteins of the DNA prereplication complexes that assemble on DNA replication origins during G_1 . The prereplication complex activates initiation of DNA replication and inhibits the assembly of new prereplication complexes. This inhibition ascertains that each chromosome is replicated only once during S phase.

G₂ Phase

RNA and protein synthesis occurs during the G_2 phase of the cell cycle. The burst of biosynthetic activity provides the substrates and enzymes to meet the metabolic requirements of the two daughter cells. Another important event that occurs during the G_2 phase of the cell cycle is repair of errors of DNA replication that may have occurred during the S phase. Failure to detect and correct these genetic errors can result in a broad spectrum of adverse consequences for the organism as well as the individual cell (1). Defects in the DNA repair mechanism have been associated with an increased incidence of cancer (2). Mitotic CdkC complexes are synthesized during the S and G_2 phase, but are inactive until DNA synthesis is completed.

M Phase

Nuclear–chromosomal division occurs during mitosis or M phase. During this phase, the cellular DNA is equally distributed to each of the daughter cells. Mitosis provides a diploid (2n) DNA complement to each somatic daughter cell. Following mitosis, eukaryotic mammalian cells contain diploid DNA reflecting a karyotype that includes 44 somatic chromosomes and a XX or XY sex chromosome complement. Exceptions to the diploid cellular content include hepatocytes (4n) and the functional syncytium of the placenta.

Mitosis is divided into prophase, metaphase, anaphase, and telophase. Mitotic CdkC complexes induce chromosome condensation during the prophase, assembly of the

mitotic spindle apparatus, and alignment of the chromosomes during the metaphase. Activation of the anaphase promoting complex (APC) leads to inactivation of the protein complexes that connect sister chromatids during metaphase, permitting the onset of anaphase. During anaphase, sister chromatids segregate to opposite spindle poles. The nuclear envelope breaks down into multiple small vesicles early in mitosis and reforms around the segregated chromosomes as they decondense during telophase. Cytokinesis is the process of division of the cytoplasm that segregates the endoplasmic reticulum and the Golgi apparatus during mitosis. After completion of mitosis, cells enter the G_1 phase and either re-enter the cell cycle or remain in G_0 .

Ploidy

After meiosis, germ cells contain a haploid (1n) genetic complement. After fertilization, a 46, XX or 46, XY diploid DNA complement is restored. Restoration of the normal cellular DNA content is crucial to normal function. Abnormalities of cellular DNA content cause distinct phenotypic abnormalities as exemplified by hydatidiform molar pregnancy (see Chapter 37). With complete hydatidiform mole, an oocyte without any nuclear genetic material (e.g., an empty ovum) is fertilized by one sperm.

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The haploid genetic content of the fertilized ovum is then duplicated and the diploid cellular DNA content is restored, resulting in a homozygous 46, XX gamete.

Less often, a complete hydatidiform mole results from the fertilization of an empty ovum by two sperm, resulting in a heterozygous 46, XX or 46, XY gamete. In complete molar pregnancies, the nuclear DNA is usually paternally derived, embryonic structures do not develop, and trophoblast hyperplasia occurs. Rarely, complete moles are biparental. This karyotype seems to be found in patients with recurrent hydatiform moles and is associated with a higher risk of persistent trophoblastic disease.

A partial hydatiform mole follows the fertilization of a haploid ovum by two sperm, resulting in a 69, XXX, 69, XXY, or 69, XYY karyotype. A partial mole contains paternal and maternal DNA, and both embryonic and placental development occur. Both the 69, YYY karyotype and the 46, YY karyotype are incompatible with embryonic and placental development. These observations demonstrate the importance of maternal genetic material, in particular the X chromosome, in normal embryonic and placental development.

In addition to total cellular DNA content, the chromosome number is an important determinant of cellular function. Abnormalities of chromosome number, which are often the result of nondisjunction during meiosis, result in well-characterized clinical syndromes such as trisomy 21 (Down syndrome), trisomy 18, and trisomy 13.

Genetic Control of the Cell Cycle

Cellular proliferation must occur to balance normal cell loss and maintain tissue and organ integrity. This process requires the coordinated expression of many genes at discrete times during the cell cycle (3). In the absence of growth factors, cultured mammalian cells are arrested in the G_0 phase. With the addition of growth factors, these quiescent cells pass through the so-called restriction point 14 to 16 hours later and enter the S phase 6 to 8 hours thereafter. **The restriction point or G_1/S boundary mark is the point at which a cell commits to proliferation. A second check point is the G_2/M boundary, which marks the point at which repair of any DNA damage must be completed (4,5,6,7).** To successfully complete the cell cycle, a number of cell division cycle (*cdc*) genes are activated.

Cell Division Cycle Genes

Among the factors that regulate the cell cycle checkpoints, proteins encoded by the *cdc2* family of genes and the cyclin proteins appear to play particularly important roles (8,9). Growth factor-stimulated mammalian cells express early-response or delayed-response genes depending on the chronological sequence of the appearance of specific RNAs. The early- and delayed-response genes act as nuclear transcription factors and stimulate the expression of a cascade of other genes. Early-response genes like *c-Jun* and *c-Fos* enhance the transcription of delayed-response genes like *E2Fs*. *E2F* transcription factors are required for the expression of various cell cycle genes and are functionally regulated by the retinoblastoma (*Rb*) protein. Binding of *Rb* to *E2F* converts *E2F* from a transcriptional activator to a repressor of transcription. Phosphorylation of *Rb* inhibits its repressing function and therefore permits *E2F*-mediated activation of genes required for entry into the S phase. Cdk4-cyclin D, Cdk6-cyclin D, and Cdk2-cyclin E complexes cause phosphorylation of *Rb*, which remains phosphorylated throughout the S, G₂ and M phases of the cell cycle. After completion of mitosis, a decline of the level of Cdk-cyclins leads to dephosphorylation of *Rb* by phosphatases and, consequently, an inhibition of *E2F* in the early G₁ phase.

As cells approach the G₁/S phase transition, synthesis of cyclin A is initiated. The Cdk2-cyclin A complex can trigger initiation of DNA synthesis by supporting the prereplication complex. The *p34 cdc2* protein and specific cyclins form a complex heterodimer referred to as *mitosis-promoting factor (MPF)*, which catalyzes protein phosphorylation and drives the cell into mitosis. Cdk1 assembles with cyclin A and cyclin B in G₂ phase and promotes the activity of the mitosis-promoting factor (MPF). **Mitosis is initiated by activation of**

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the *cdc* gene at the G₂/M checkpoint (10,11). Once the G₂/M checkpoint has been passed, the cell undergoes mitosis. In the presence of abnormally replicated chromosomes, progression past the G₂/M checkpoint does not occur.

The *p53* tumor suppressor gene participates in cell cycle control. Cells exposed to radiation therapy exhibit an S-phase arrest that is accompanied by increased expression of *p53*. This delay permits the repair of radiation-induced DNA damage. With mutations of *p53*, the S-phase arrest that normally follows radiation therapy does not occur (12,13). The wild type *p53* gene can be inactivated by the human papillomavirus E6 protein, preventing S-phase arrest in response to DNA damage (14).

Apoptosis

The regulation and maintenance of normal tissue requires a balance between cell proliferation and programmed cell death, or apoptosis. When proliferation exceeds programmed cell death, the result is hyperplasia. When programmed cell death exceeds proliferation, the result is atrophy. Programmed cell death is a crucial concomitant of normal embryologic development. This mechanism accounts for deletion of the interdigital webs (15), palatal fusion (16), and development of the intestinal mucosa (17). Programmed cell death is also an important phenomenon in normal physiology (18). The reduction in the number of endometrial cells following alterations in steroid hormone levels during the menstrual cycle is, in part, a consequence of programmed cell death (19,20). In response to androgens, granulosa cells undergo programmed cell death (e.g., follicular atresia) (21).

Programmed cell death, or apoptosis, is an energy-dependent, active process that is initiated by the expression of specific genes. This process is distinct from cell necrosis, although both mechanisms result in a reduction in total cell number. In programmed

cell death, cells shrink and undergo phagocytosis. Apoptosis is an energy-dependent process that results from the expression of specific genes. Conversely, groups of cells expand and lyse when undergoing cell necrosis. The process is energy-independent and results from noxious stimuli. Programmed cell death is triggered by a variety of factors, including intracellular signals and exogenous stimuli such as radiation exposure, chemotherapy, and hormones. Cells undergoing programmed cell death may be identified on the basis of histologic, biochemical, and molecular biologic changes. Histologically, apoptotic cells exhibit cellular condensation and fragmentation of the nucleus. Biochemical correlates of impending programmed cell death include an increase in transglutaminase expression and fluxes in intracellular calcium concentration (22).

Programmed cell death has recently emerged as an important factor in the growth of neoplasms. Historically, neoplastic growth has been characterized by uncontrolled cellular proliferation that resulted in a progressive increase in tumor burden. It is now recognized that **the increase in tumor burden associated with progressive disease reflects an imbalance between cell proliferation and cell death.** Cancer cells not only fail to respond to the normal signals to stop proliferating, but they may also fail to recognize the physiologic signals that trigger programmed cell death.

Modulation of Cell Growth and Function

The normal cell exhibits an orchestrated response to the changing extracellular environment. The three groups of substances that signal these extracellular changes are steroid hormones, growth factors, and cytokines. The capability to respond to these stimuli requires a cell surface recognition system, intracellular signal transduction, and nuclear responses for the expression of specific genes in a coordinated fashion. **Among the genes that participate in control of cell growth and function, *proto-oncogenes* and *tumor suppressor genes* are particularly important.** More than 100 proto-oncogene products that contribute to growth regulation have been identified (23) (Table 6.1). As a group, proto-oncogenes exert positive effects upon cellular proliferation. In contrast, *tumor suppressor genes* exert inhibitory regulatory effects on cellular proliferation (Table 6.2).

Table 6.1 Protooncogenes	
<i>Protooncogenes</i>	<i>Gene Product/Function</i>
	<i>Growth factors</i>
	Fibroblast growth factor
<i>fgf-5</i>	
<i>Sis</i>	Platelet-derived growth factor beta
<i>hst, int-2</i>	
	<i>Transmembrane receptors</i>
<i>erb-B</i>	Epidermal growth factor (EGF) receptor
<i>HER-2/neu</i>	EGF-related receptor
<i>Fms</i>	Colony-stimulating factor (CSF) receptor
<i>Kit</i>	Stem cell receptor
<i>Trk</i>	Nerve growth factor receptor
	<i>Inner-membrane receptor</i>
<i>bcl-2</i>	
<i>Ha- ras, N-ras, N- ras</i>	

*fgr, lck, src, yes***Cytoplasmic messengers***Crk**cot, plm-1, mos, raf/mil***Nuclear DNA binding proteins***erb-B1**jun, ets-1, ets-2, fos, gil 1, rel, ski, vav**lyl-1, maf, myb, myc, L- myc, N- myc, evi-1*

Steroid Hormones

Steroid hormones play a crucial role in reproductive biology as well as in general physiology. Among the various functions, steroid hormones influence pregnancy, cardiovascular function, bone metabolism, and an individual's sense of general well-being. The action of steroid hormones is mediated via extracellular signals to the nucleus to affect a physiologic response.

Estrogens exert a variety of effects on growth and development of different tissues. The effects of estrogens are mediated via estrogen receptors (ER), intracellular proteins that function as ligand-activated transcription factors and belong to the nuclear receptor superfamily (24). Two mammalian ERs have been identified, denoted ER α and ER β . The structure of both receptors is similar and consists of six domains named A through F from the N- to C-terminus, encoded by 8 to 9 exons (25).

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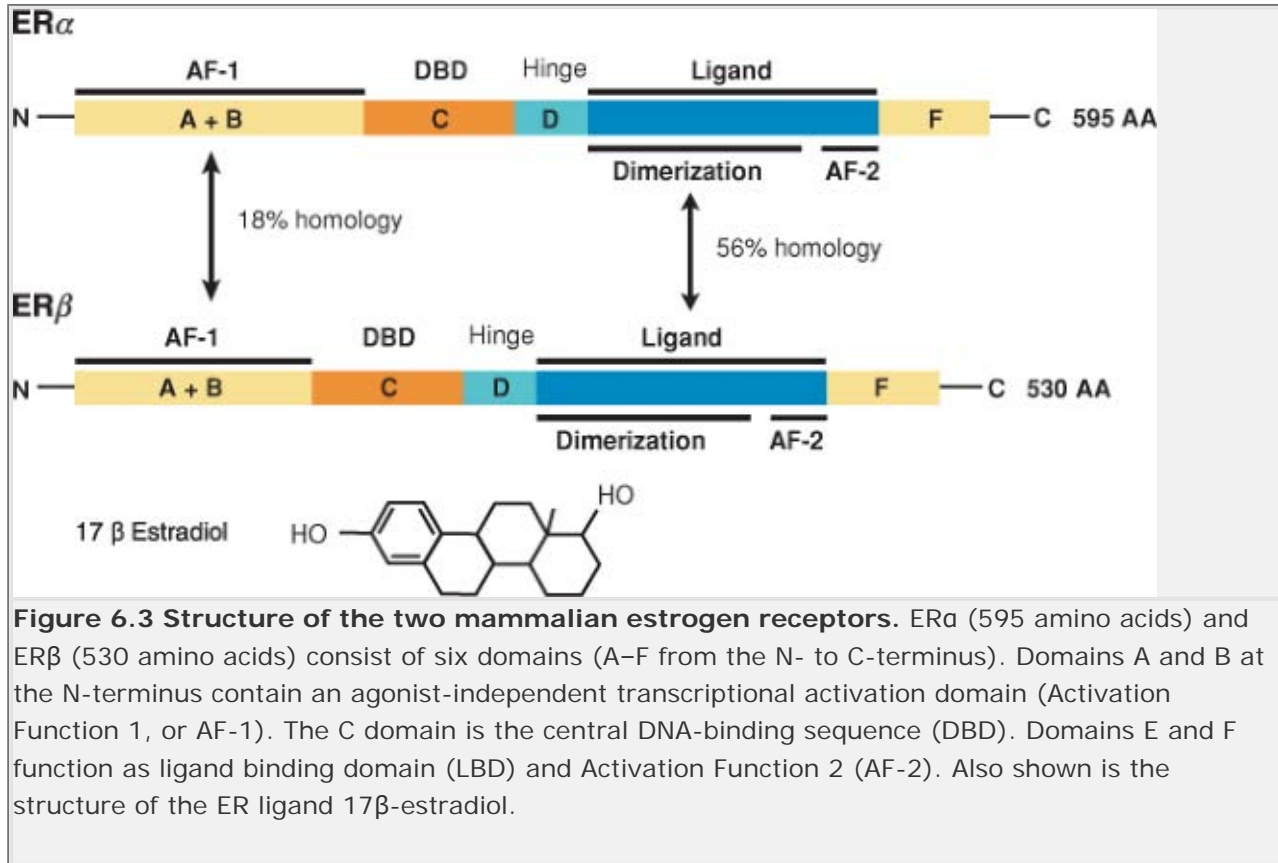
Table 6.2 Tumor Suppressor Genes

p53	Mutated in as many as 50% of solid tumors
Rb	Deletions and mutations predispose to retinoblastoma
PTEN	Dual specificity phosphatase that represses PI3-kinase/Akt pathway activation with negative effect on cell growth
P16^{INK4a}	Binds to cyclin-CDK4 complex inhibiting cell cycle progression
FHIT	Fragile histidine triad gene with tumor suppressor function via unknown mechanisms
WT1	Mutations are correlated with Wilms' tumor
NF1	Neurofibromatosis gene
APC	Associated with colon cancer development in patients with familial adenomatous

Domains A and B are located at the N-terminus and contain an agonist-independent transcriptional activation domain (Activation Function 1, or AF-1). The C domain is a highly conserved central DNA-binding domain composed of two zinc fingers through which ER interacts with the major groove and the phosphate backbone of the DNA helix. The C-terminus of the protein contains domains E and F and functions as ligand-binding domain (LBD—domain E) and Activation Function 2 (AF-2—domain F) (Fig. 6.3).

Activation of transcription via the estrogen receptor is a multistep process. The initial step requires activation of the ER via various mechanisms (Fig. 6.4). For example, estrogens such as 17 β -estradiol can diffuse into the cell and bind to the LBD of the ER. Upon ligand binding, the ER undergoes conformational changes followed by a dissociation of various bound proteins,

mainly heat shock proteins 90 and 70 (*hsp90* and *hsp70*). Activation of the R also requires phosphorylation by several protein kinases, including casein kinase II, protein kinase A, and components of the Ras/MAP kinase pathway (26). Four phosphorylation sites of the ER are clustered in the NH₂ terminus with the AF-1 region.



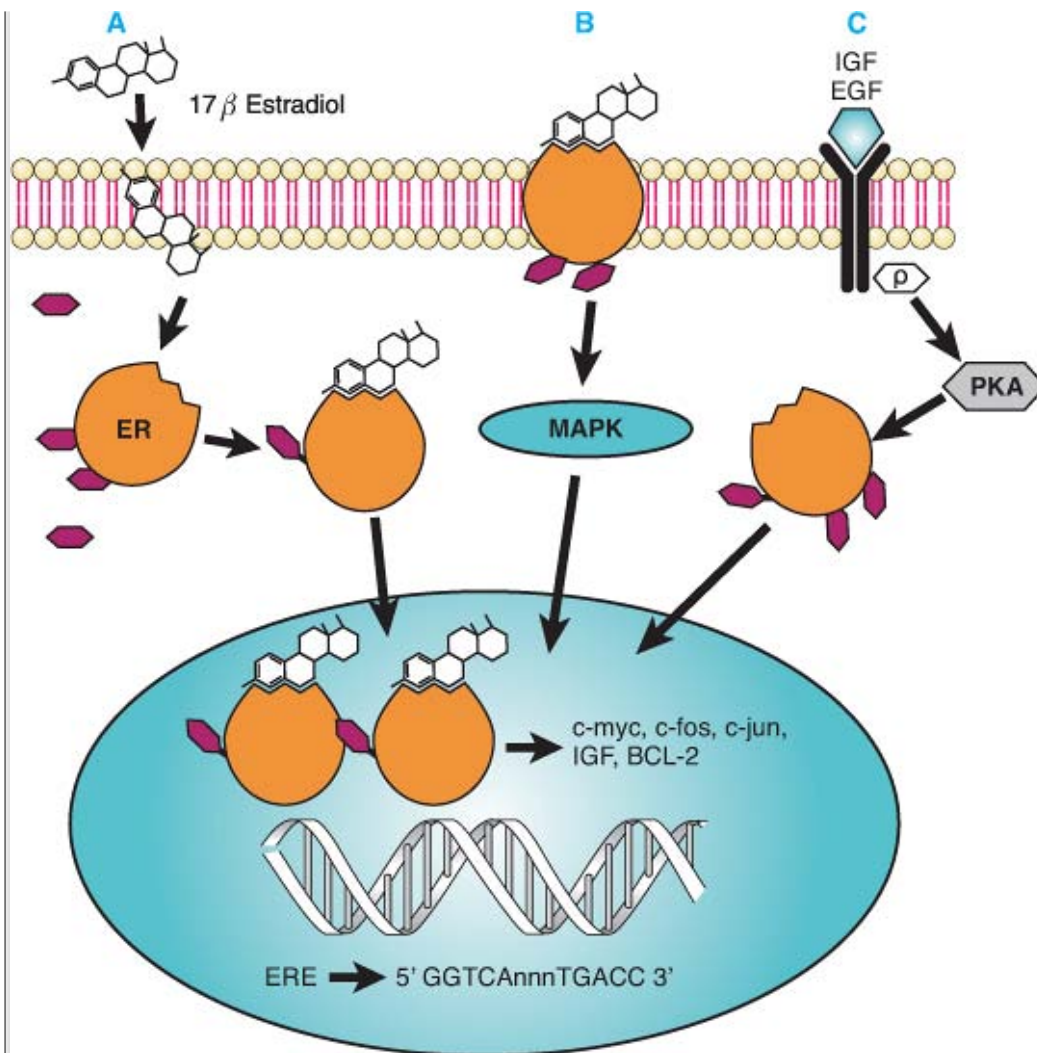


Figure 6.4 Activation of estrogen receptor mediated transcription. Intracellular estrogen receptor signaling is mediated via different pathways. A: 17β-estradiol diffuses through the cell membrane and binds to cytoplasmic ER. The ER is subsequently phosphorylated, undergoes dimerization, and binds to the estrogen response element (ERE) on the promoter of an estrogen responsive gene. **B:** Estrogen ligand binds to membrane-bound ER and activates the mitogen-activated protein kinase (MAPK) pathways that support ER-mediated transcription. **C:** Binding of cytokines such as insulinlike growth factor (IGF) or epidermal growth factor to their membrane receptor can cause activation of protein kinases like PKA, which subsequently activates ER by phosphorylation.

The activated ER elicits a number of different genomic as well as nongenomic effects on intracellular signaling pathways.

The classical steroid signaling pathway involves binding of the activated estrogen receptor to an estrogen responsive element (ERE) on the genome as homodimers and subsequent stimulation of transcription (27). The minimal consensus sequence for the ERE is a 13 bp palindromic inverted repeat (IR) and is defined as 5'-GGTCAnnnTGACC-3'. Genes that are regulated by activated ERs include early gene responses such as *c-myc*, *c-fos*, and *d-jun*, as well as genes encoding for growth factors such as insulin growth factor (IGF-1 and IGF-2), epidermal growth factor (EGF), transforming growth factor-α, and colony-stimulating factor (CSF-1).

In addition to the described genomic effects of estrogens, there is growing evidence for nongenomic effects of estrogens on intracellular signal transduction pathways.

These effects include, for example, rapid activation of the adenylate cyclase, which results in

cyclic adenosine monophosphate (cAMP)–dependent activation of protein kinase A (PKA) (28). Estrogens can also stimulate the mitogen-activated protein kinase (MAPK) pathways and rapidly activate the Erk1/Erk2 proteins.

Various ligands with different affinities to the ER have been developed and are called *selective estrogen receptor modulators (SERMs)*. *Tamoxifen*, for example, is a mixed agonist/antagonist for ER α but it is a pure antagonist for ER β . The ER β receptor is ubiquitously expressed in hormone-responsive tissues, whereas the expression of ER α fluctuates in response to the hormonal milieu. The cellular and tissue effects of an estrogenic compound appear to reflect a dynamic interplay between the actions of these estrogen receptor isoforms. These observations underscore the complexity of estrogen interactions with both normal and neoplastic tissue. Mutations of hormone receptors and their functional consequences illustrate their important contributions to normal physiology. For example, absence of ER α in a male human has been reported (29). The clinical sequelae attributed to this mutation include incomplete epiphyseal closure, increased bone turnover, tall stature, and impaired glucose tolerance. The androgen insensitivity syndrome is caused by mutations of the androgen receptor (30). Mutations of the receptors for growth hormone and thyroid-stimulating hormone result in a spectrum of phenotypic alterations. Mutations of hormone receptors may also contribute to the progression of neoplastic disease and resistance to hormone therapy (31,32).

Growth Factors

Growth factors are polypeptides that are produced by a variety of cell types and exhibit a wide range of overlapping biochemical actions. Growth factors bind to high-affinity cell membrane receptors and trigger complex positive and negative signaling pathways that regulate cell proliferation and differentiation (33). **In general, growth factors exert positive or negative effects upon the cell cycle by influencing gene expression related to events that occur at the G₁/S cell cycle boundary (34).**

Because of their short half-life in the extracellular space, growth factors generally act over limited distances through autocrine or paracrine mechanisms. In the autocrine loop, the growth factor acts on the cell that produced it. The paracrine mechanism of growth control involves the effect of growth factors on another cell in proximity. Growth factors that play an important role in female reproductive physiology are listed in Table 6.3. The biologic response of a cell to a specific growth factor depends on a variety of factors, including the cell type, the cellular microenvironment, and the cell cycle status.

The regulation of ovarian function occurs through *autocrine, paracrine, and endocrine mechanisms* (35,36,37,38,39,40,41). The growth and differentiation of ovarian cells are particularly influenced by the insulinlike growth factors (IGF) (Fig. 6.5). Insulinlike growth factors amplify the actions of gonadotropin hormones on autocrine and paracrine growth factors found in the ovary. The IGF-1 acts on granulosa cells to cause an increase in cAMP, progesterone, oxytocin, proteoglycans, and inhibin. On theca cells, IGF-1 causes an increase in androgen production. Theca cells produce tumor necrosis factor- α (TNF- α) and EGF, which are regulated by follicle-stimulating hormone (FSH). Epidermal growth factor acts on granulosa cells to stimulate mitogenesis. Follicular fluid contains IGF-1, IGF-2, TNF- α , TNF- β , and EGF. **Disruption of these autocrine and paracrine intraovarian pathways may be the basis of polycystic ovarian disease, disorders of ovulation, and ovarian neoplastic disease.**

Transforming growth factor (TGF)- β activates intracytoplasmic serine threonine kinases and inhibits cells in the late G₁ phase of the cell cycle (41). It appears to play an important role

in embryonic remodeling. Müllerian-inhibiting substance (MIS), which is responsible for regression of the müllerian duct, is structurally and functionally related to TGF- β (42). Transforming growth factor α is an EGF homologue that binds to the EGF receptor and acts as an autocrine factor in normal cells. As with EGF, TGF- α promotes entry of G_0 cells into the G_1 phase of the cell cycle. The role of growth factors in endometrial growth and function has been the subject of several reviews (36,37,38,39,40,41). Similar to the ovary, autocrine, paracrine, and endocrine mechanisms of control also occur in endometrial tissue.

Growth Factor	Sources	Targets	Actions
Platelet-derived growth factor (PDGF)	Placenta, platelets, preimplantation embryo, endothelial cells	Endothelial cells Trophoblasts	Mitogen
Epidermal growth factor (EGF)	Submaxillary gland, theca cells Granulosa cells Endometrium	Mitogen	
Transforming growth factor-α (TGF-α)	Embryo, placenta, theca cell, ovarian stromal cell	Placenta Granulosa cells	Mitogen
Transforming growth factor-β (TGF-β)	Embryo, theca cells Endometrium Granulosa cells Theca cells	Mitogen	
Insulinlike growth factor 1 (IGF-1)	Granulosa cells	Theca cells Granulosa cells	Mediates growth hormone activity
Insulinlike growth factor 2 (IGF-2)	Theca cells	Theca cells	Insulinlike
Fibroblast growth factor (FGF)	Granulosa cells	Granulosa cells Angiogenic Mitogen	

Intracellular Signal Transduction

Growth factors trigger intracellular biochemical signals by binding to cell membrane receptors. In general, these membrane-bound receptors are *protein kinases* that convert an extracellular signal into an intracellular signal. The interaction between growth factor ligand and its receptor results in receptor dimerization, autophosphorylation, and tyrosine kinase activation. Activated receptors in turn phosphorylate substrates in the cytoplasm and trigger the intracellular signal transduction system (Fig. 6.6). The intracellular signal transduction system relies on serine threonine kinases, *src*-related kinases, and G proteins. Intracellular signals activate nuclear factors that regulate gene expression. **Many of the proteins that participate in the intracellular signal transduction system are encoded by proto-oncogenes that are divided into subgroups based on their cellular location or enzymatic function** (43,44) (Fig. 6.7).

The *raf* and *mos* proto-oncogenes encode proteins with serine threonine kinase activity. These kinases integrate signals originating at the cell membrane with those that are forwarded to the nucleus (45,46). Protein kinase C (PKC) is an important component of a second messenger system that exhibits serine threonine kinase activity. This enzyme plays a central role in phosphorylation, which is a general mechanism for activating and deactivating proteins. It

also plays an important role in cell metabolism and division (47).

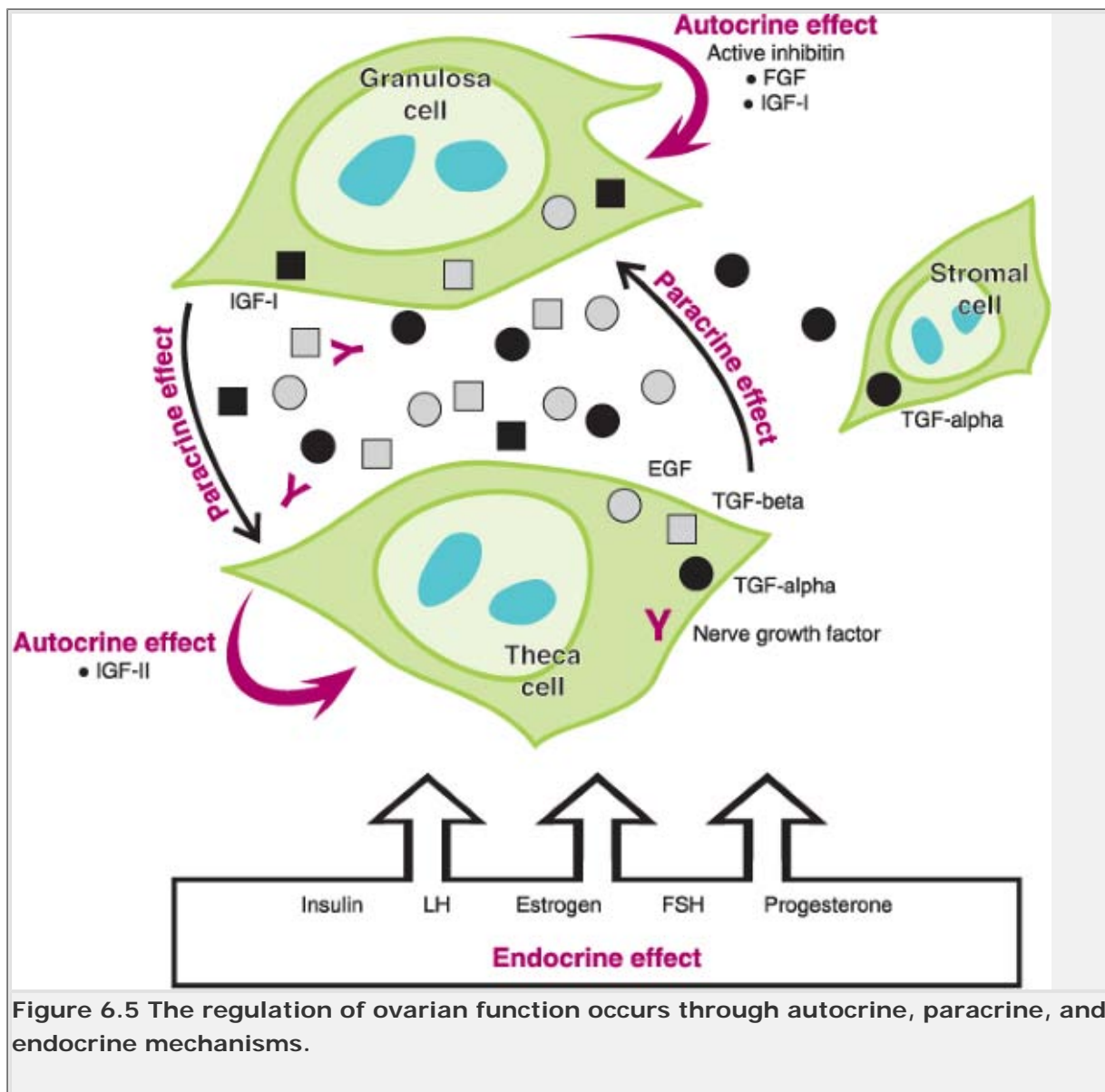


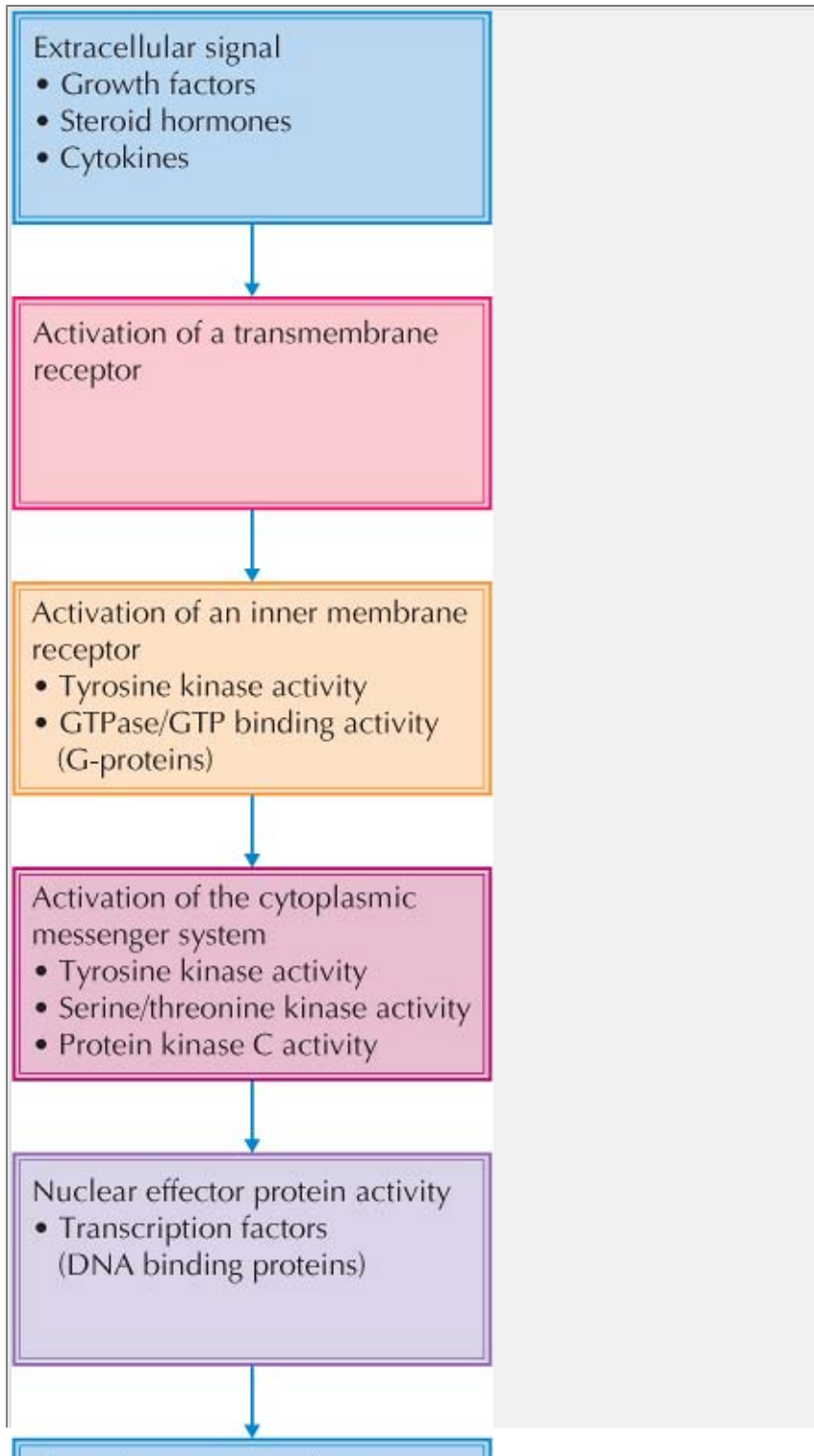
Figure 6.5 The regulation of ovarian function occurs through autocrine, paracrine, and endocrine mechanisms.

The *Scr* family of tyrosine kinases is related to PKC and includes protein products encoded by the *scr*, *yes*, *fgr*, *hck*, *lyn*, *fyn*, *lck*, *alt*, and *fps/fes* proto-oncogenes. These proteins bind to the inner cell membrane surface.

The *G proteins* are guanyl nucleotide-binding proteins. The heterotrimeric or large G proteins link receptor activation with effector proteins such as adenylyl cyclase, which activates the cAMP-dependent, kinase-signaling cascade (48). The monomeric or small G proteins, encoded by the *ras* proto-oncogene family, are designated *p21* and are particularly important regulators of mitogenic signals. The *p21 Ras* protein exhibits guanyl triphosphate (GTP) binding and GTPase activity. Hydrolysis of GTP to guanyl diphosphate (GDP) terminates *p21 Ras* activity. The *p21 Ras* protein influences the production of deoxyguanosine (dG) and inositol phosphate (IP) 3, arachidonic acid production, and IP turnover.

The phosphoinositide 3 (PI3) kinase can be activated by various growth factors like platelet-derived growth factor (PDGF) or IGF results. Activation of PI3-kinase results in an increase of intracellular, membrane-bound lipids, phosphatidylinositol-(3,4)-diphosphate (PIP2), and phosphatidylinositol-(3,4,5)-triphosphate (PIP3). The *Akt* protein is

subsequently phosphorylated by PIP3-dependent kinases (PDK) for full activation. Activated *Akt* is released from the membrane and elicits downstream effects that lead to an increase in cell proliferation, prevention of apoptosis, invasiveness, drug resistance, and neoangiogenesis (49). The *PTEN* (phosphatase and chicken tensin homologue deleted on chromosome 10) protein is an important factor in the phosphoinositide 3 (PI3)-kinase pathway, because it counteracts the activation of *Akt* by dephosphorylating PIP3. Cells with mutated tumor suppressor gene *PTEN* and lack of functional *PTEN* expression display an increased proliferation rate and decreased apoptosis, therefore possibly supporting the development of a malignant phenotype. *PTEN* is frequently mutated in endometrioid adenocarcinoma. Furthermore, lack of functional *PTEN* expression has been described in endometriosis.



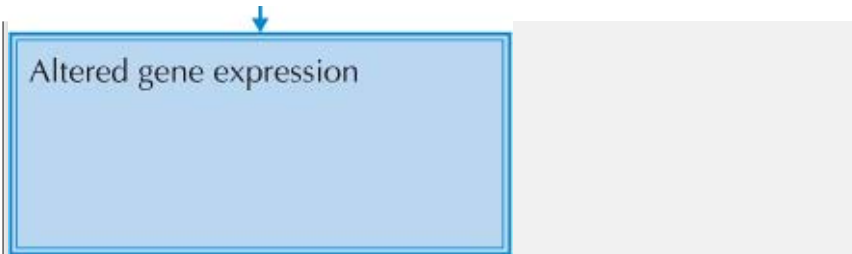


Figure 6.6 Pathways of intracellular signal transduction.

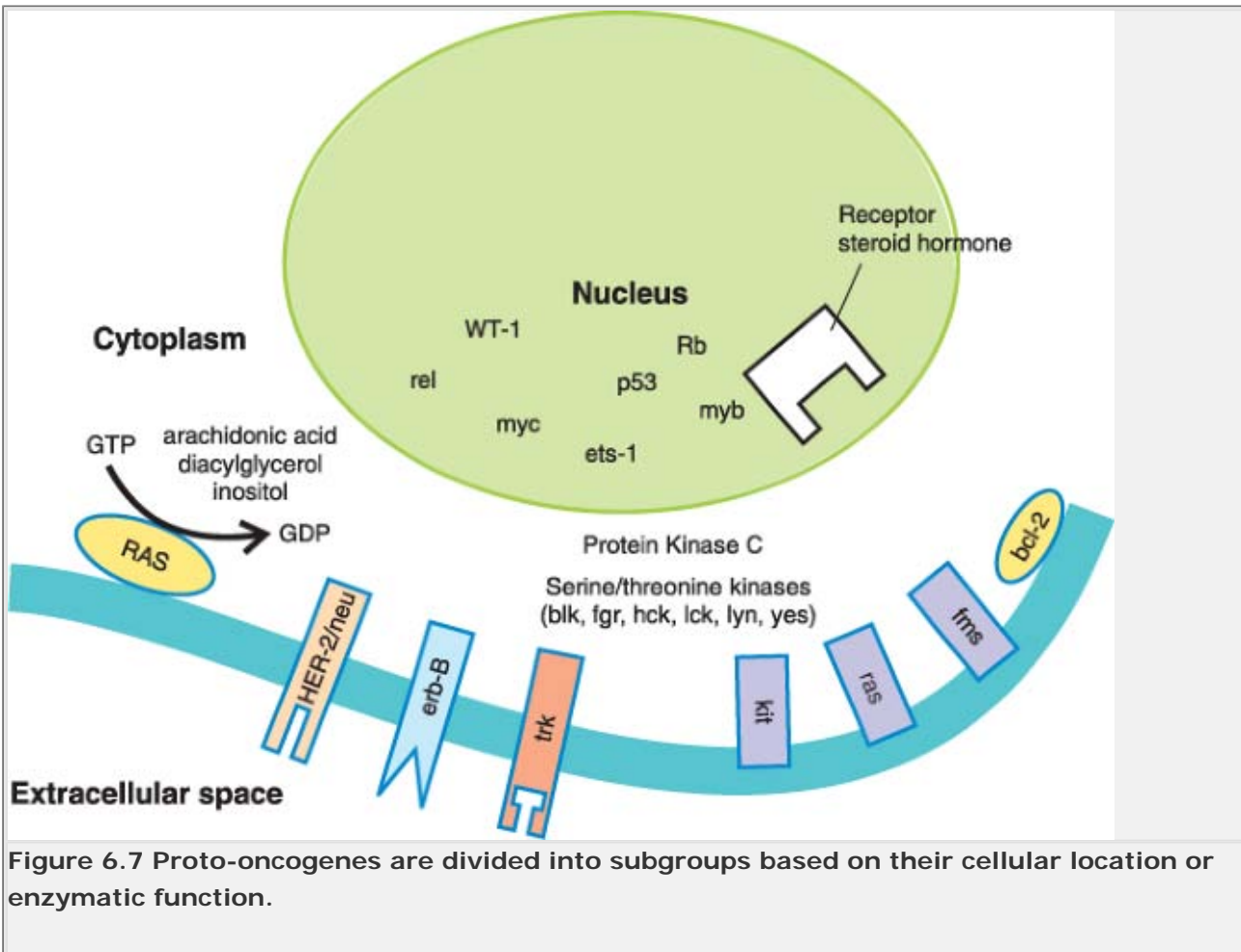


Figure 6.7 Proto-oncogenes are divided into subgroups based on their cellular location or enzymatic function.

Gene Expression

Regulation of genetic transcription and replication is crucial to the normal function of the daughter cells as well as the tissues and ultimately the organism. Transmission of external signals to the nucleus by way of the intracellular signal transduction cascade culminates in the transcription and translation of specific genes that ultimately affect the structure, function, and proliferation of the cell.

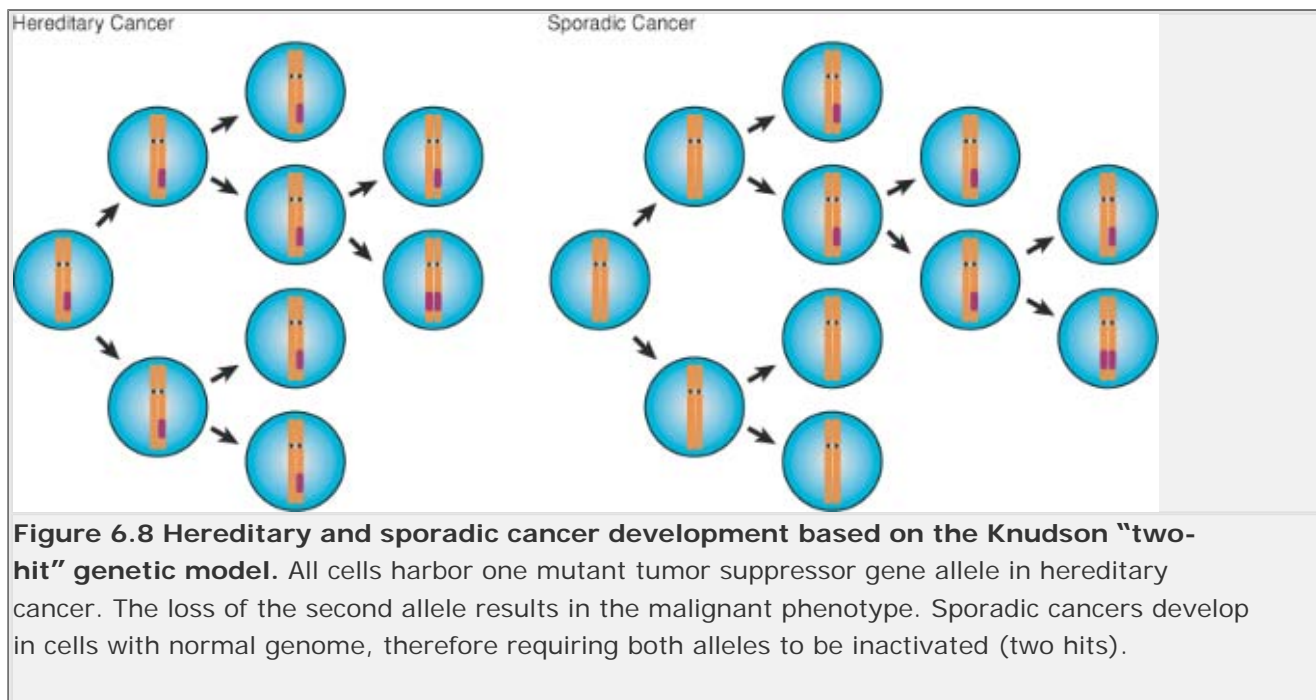
The human genome project has resulted in the determination of the sequence of DNA of the entire human genome. With the completion of this project, it appears that the human genetic complement consists of approximately 30,000 genes. Sequencing the human genome is a major scientific achievement that opens the door for more detailed studies of structural and functional genomics. **Structural genomics involves the study of three-dimensional structures of proteins based on their amino acid sequences.**

Functional genomics provides a way to correlate structure and function. Proteomics involves the identification and cataloging of all proteins used by a cell, and cytomics involves the study of cellular dynamics, including intracellular system regulation and response to external stimuli. Each of these areas of investigation requires an understanding of basic genetic alterations.

Cancer Genetics

Cancer is a genetic disease that results from a series of mutations in various cancer genes. Uncontrolled cell growth occurs because of accumulation of somatic mutations or the inheritance of one or more mutations through the germline followed by additional somatic mutations. The mutation in genes that are directly involved in normal cellular growth and proliferation can lead to the development of uncontrolled growth, invasion, and metastasis.

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According to the Knudson hypothesis, which was first described in children with hereditary retinoblastoma, two hits or mutations within the genome of a cell are required for a malignant phenotype to develop (50). In hereditary cancers, the first hit is present in the genome of every cell. Only one additional hit is necessary, therefore, to disrupt the correct function of the second cancer gene allele. In contrast, sporadic cancers develop in cells without hereditary mutations in the cancer predisposing alleles. In this case, both hits must occur in a single somatic cell to disrupt both cancer gene alleles (Fig 6.8).

Most adult solid tumors require 5 to 10 rate-limiting mutations to acquire the malignant phenotype. Among these mutations, some are responsible for causing the cancer phenotype, whereas others might be considered bystander mutations, as with, for example, the amplification of genes that are adjacent to an oncogene. The most compelling evidence for the mutagenic tumor development process is that the age-specific incidence rates for most human epithelial tumors increase at roughly the fourth to eighth power of elapsed time.

Gatekeepers and Caretakers

Cancer susceptibility genes are divided into "gatekeepers" and "caretakers" (51). Gatekeeper genes control cellular proliferation and are divided into oncogenes and tumor suppressor genes. In general, oncogenes stimulate cell growth and proliferation, and tumor suppressor genes reduce the rate of cell proliferation or induce apoptosis. Gatekeepers prevent the development of tumors by inhibiting growth or promoting cell death. Examples of gatekeeper genes include the tumor suppressor genes *p53* and the retinoblastoma gene.

Caretaker genes preserve the integrity of the genome and are involved in DNA repair (stability genes). The inactivation of caretakers increases the likelihood of persistent mutations

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in gatekeeper genes and other cancer-related genes. The DNA mismatch repair genes *MLH1*, *MSH2*, and *MSH6* are examples of a caretaker gene.

Hereditary Cancer

Most cancers are caused by spontaneous somatic mutations. However, a small percentage of cancers arise on a heritable genomic background. About 12% of all ovarian cancers and about 5% of endometrial cancers are considered to be hereditary (52,53). Germline mutations in general require additional mutations at one or more loci for tumorigenesis to occur. These mutations occur via different mechanisms, for example, via environmental factors such as ionizing radiation or mutations of stability genes.

Characteristics of hereditary cancers include diagnosis at a relatively early age and a family history of cancer, usually of a specific cancer syndrome, in two or more relatives. Hereditary cancer syndromes associated with gynecologic tumors are summarized in Table 6.4.

Various cancer-causing genetic and epigenetic mechanisms have been described. On the genomic level, gain of function gene mutations can lead to a conversion of proto-oncogenes into oncogenes, and loss of function gene mutations can inactivate tumor-suppressor genes. Epigenetic changes include DNA methylation, which can cause inactivation of tumor suppressor gene expression by preventing the correct function of the associated promoter sequence. Collectively, these genetic and epigenetic changes are responsible for the development of cancer characterized by the ability of cells to invade and metastasize, grow independently of growth factor support, and escape from antitumor immune responses.

Table 6.4 Hereditary Cancer Syndromes Associated with Gynecologic Tumors

<i>Hereditary Syndrome</i>	<i>Gene Mutation</i>	<i>Tumor Phenotype</i>
Li-Fraumeni syndrome	TP53, CHEK2	Breast cancer, soft tissues sarcoma, adrenal cortical carcinoma, brain tumors
Cowden syndrome, Bannayan-Zonana syndrome	PTEN	Breast cancer, hamartoma, glioma, endometrial cancer
Hereditary breast and ovarian cancer	BRCA1, BRCA2	Cancer of breast, ovary, fallopian tube
Hereditary nonpolyposis colorectal cancer (HNPCC)	MLH1, MSH2, MSH3, MSH6, PMS2	Cancer of colon, endometrium, ovary, stomach, small bowel, urinary tract
Multiple endocrine neoplasia type I	Menin	Cancer of thyroid, pancreas and pituitary, ovarian carcinoma

Multiple endocrine neoplasia type II	RET	Cancer of thyroid and parathyroid, pheochromocytoma, ovarian carcinoid
Peutz-Jeghers syndrome	STK11	Gastrointestinal hamartomatous polyps, tumors of the stomach, duodenum, colon, ovarian sex cord tumor with annular tubules (SCTAT)

Oncogenes

Oncogenes comprise a family of genes that result from gain of function mutations of their normal counterparts, proto-oncogenes. The normal function of proto-oncogenes is to stimulate proliferation in a controlled context. Activation of oncogenes can lead to stimulation of cell proliferation and development of a malignant phenotype.

Oncogenes were initially discovered through retroviral tumorigenesis. Viral infection of mammalian cells can result in integration of the viral sequences into the proto-oncogene sequence of the host cell. The integrated viral promoter activates transcription from the surrounding DNA sequences, including the proto-oncogene. Enhanced transcription of the proto-oncogene sequences results in the overexpression of growth factors, growth factor receptors, and signal transduction proteins that result in stimulation of cell proliferation. One of the most important group of viral oncogenes is the family of *ras* genes, which include *c-H (Harvey)-ras*, *c-K (Kirsten)-ras*, and *N (Neuroblastoma)-ras*.

Tumor Suppressor Genes

Tumor suppressor genes are involved in the development of most cancers and are usually inactivated in a two-step process in which both copies of the tumor suppressor gene are mutated or inactivated by epigenetic mechanisms like methylation (54). The most commonly mutated tumor suppressor gene in human cancers is *p53* (55). The *p53* protein regulates transcription of other genes involved in cell cycle arrest such as *p21*. Upregulation of *p53* expression is induced by DNA damage and contributes to cell cycle arrest, allowing DNA repair to occur. *p53* also plays an important role in the initiation of apoptosis. Interestingly, the most common mechanism of inactivation of *p53* differs from the classic two-hit model. In most cases, missense mutations that change a single amino acid in the DNA binding domain of *p53* results in overexpression of nonfunctional *p53* protein in the nucleus of the cell.

The identification of tumor-suppressor genes has been facilitated by positional cloning strategies. The main approaches are cytogenetic studies to identify chromosomal alterations in tumor specimens, DNA linkage techniques to localize genes involved in inherited predisposition to cancer, and examination for loss of heterozygosity or allele among studies in sporadic tumors. Comparative genomic in situ hybridization (CGH) allows fluorescence identification of chromosome gain and loss in human cancers within a similar experiment.

Stability Genes

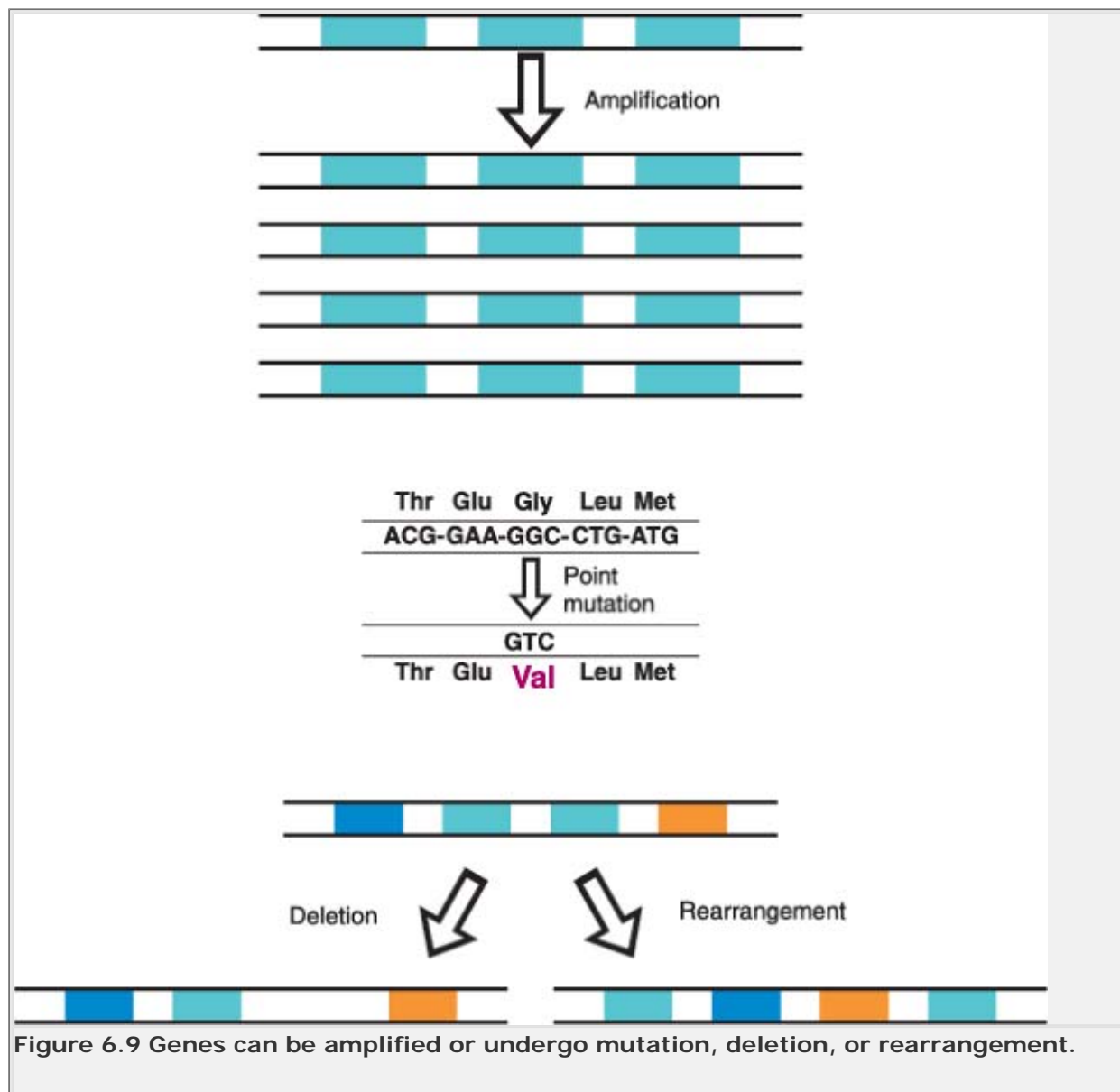
The third class of cancer genes is "stability genes," which promote tumorigenesis in a way different from tumor suppressor genes or amplified oncogenes. The function of stability genes is mainly the preservation of the correct DNA sequence during DNA replication (caretaker function) (56). Mistakes that are made during normal

DNA replication or induced by exposure to mutagens can be repaired by a variety of mechanisms that involve mismatch repair genes, nuclear-type excision repair genes, and base excision repair genes. The inactivation of stability genes leads to a higher mutation rate in potentially all genes. However, only mutations in oncogenes and tumor-suppressor genes influence cell proliferation and confer a selective growth advantage to the mutant cell. Similar to tumor-suppressor genes, both alleles of stability genes must be activated to cause loss of function.

Genetic Aberrations

Gene replication, transcription, and translation are imperfect processes, and the fidelity is less than 100%. Genetic errors may result in abnormal structure and function of genes and proteins. Genomic alterations such as gene amplification, point mutations, and deletions or rearrangements have been identified in premalignant, malignant, and benign neoplasms of the female genital tract (57) (Fig. 6.9).

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Amplification

Amplification refers to an increase in the copy number of a gene. Amplification results in enhanced gene expression by increasing the amount of template DNA that is available for transcription. Proto-oncogene amplification is a relatively common event in malignancies of the female genital tract. The *HER2/Neu* proto-oncogene, also known as *c-erbB-2* and *HER2*, encodes a 185 *kDa* transmembrane glycoprotein with intrinsic tyrosine kinase activity. It belongs to a family of transmembrane receptor genes that includes the epidermal growth factor receptors (*erbB-1*), *erbB-3*, and *erbB-4*. *HER2/Neu* interacts with a variety of different cellular proteins that in general increase cell proliferation. Overexpression of *HER2/neu* has been demonstrated in about 30% of breast cancers, 20% of advanced ovarian cancers, and as many as 50% of endometrial cancers (58). High tissue expression of *HER2/neu* is correlated with a decreased overall survival particularly in patients with endometrial cancer.

Point Mutations

Point mutations of a gene may remain without any consequence for the expression and function of the protein (gene polymorphism). However, point mutations can alter a codon sequence and subsequently disrupt the normal function of a gene product. The *ra* gene family is an example of oncogene-encoded proteins that disrupt the intracellular signal transduction system following point mutations. Transforming Ras proteins contain point mutations in critical codons (i.e., codons 11, 12, 59, 61) with decrease of GTPase activity and subsequent expression of constitutively active Ras. Point mutations of the *p53* gene are the most common genetic mutations described in solid tumors.

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These mutations occur at preferential "hot spots" that coincide with the most highly conserved regions of the gene. The *p53* tumor suppressor gene encodes for a phosphoprotein that is generally detectable in the nucleus of normal cells. When DNA damage occurs, *p53* can arrest cell cycle progression to allow the DNA to be repaired or undergo apoptosis. The lack of function of normal *p53* within a cancer cell results in a loss of control of cell proliferation with inefficient DNA repair and genetic instability. Mutations of the *p53* gene occur in approximately 50% of advanced ovarian cancers and 30% to 40% of endometrial cancers but are uncommon in cervical cancer.

Point mutations in the *BRCA1* and *BRCA2* genes can alter the activity of these genes and predispose to the development of breast and ovarian cancer (59). The frequency of *BRCA1* and *BRCA2* mutations in the general population in the United States is estimated at 1:250. Specific founder mutations have been reported for various ethnic groups. For example, two *BRCA1* mutations (185delAG and 5382insC) and one *BRCA2* mutation (6174delT) are found in 2.5% of Ashkenazi Jews of Central and Eastern European descent. Additional founder mutations have been described in other ethnic groups, including from the Netherlands (*BRCA1* 2804delAA and several large deletion mutations), Iceland (*BRCA2*, 995del5), and Sweden (*BRCA1*, 3171ins5).

The *BRCA* proteins are involved in DNA repair. If DNA is damaged, for example, by ionizing radiation or chemotherapy, the *BRCA2* protein binds to the *RAD51* protein, which is central for the repair of double-stranded breaks via homologous recombination. *BRCA2* regulates the availability and activity of *RAD51* in this key reaction. Phosphorylation of the *BRCA2/RAD51* complex allows *RAD51* to bind to the site of DNA damage and, in conjunction with several other proteins, mediates repair of DNA by homologous recombination. *BRCA1* functions within a complex network of protein-protein interactions mediating DNA repair by homologous recombination and regulating transcription via the *BRCA1* associated surveillance complex (BASC).

Deletions and Rearrangements

Deletions and rearrangements reflect gross changes in the DNA template that may result in the synthesis of a markedly altered protein product. Somatic mutations may involve chromosomal translocations that result in chimeric transcripts with juxtaposition of one gene to the regulatory region of another gene. This mutation type is most commonly reported in leukemias, lymphomas, and mesenchymal tumors. The Philadelphia chromosome in chronic myeloid leukemia, for example, is the result of a reciprocal translocation between one chromosome 9 and one chromosome 22. The DNA sequence removed from chromosome 9 contains the proto-oncogene *c-ABL* and inserts into the *BCR* gene sequence on chromosome 22 (Philadelphia chromosome). The resulting chimeric *BCR-ABL* gene product functions as a constitutively active tyrosine kinase and stimulates cellular proliferation by such mechanisms as an increase of growth factors.

Immunology

The immune system plays an essential part in host defense mechanisms, in particular in response to infections and neoplastic transformation. Our increased understanding of immune system regulation has provided opportunities for the development of novel immunotherapeutic and immunodiagnostic approaches.

Immunologic Mechanisms

The human immune system has the potential to respond to abnormal or tumor cells in various ways. Some of these immune responses occur in an innate or antigen-nonspecific manner, whereas others are adaptive or antigen specific.

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Adaptive responses are specific to a given antigen. The establishment of a memory response allows a more rapid and vigorous response to the same antigen in future encounters. Various innate and adaptive immune mechanisms are involved in responses to tumors, including cytotoxicity directed to tumor cells mediated by cytotoxic T cells, natural killer (NK) cells, macrophages, and antibody-dependent cytotoxicity mediated by complementation activation (60).

Adaptive or specific immune responses include humoral and cellular responses.

Humoral immune responses refer to the production of antibodies. Antibodies are bifunctional molecules composed of specific antigen-binding sites for interaction with foreign antigens. They are associated with a constant region that directs the biologic activities of the antibody, such as binding to phagocytic cells or activation of complement. **Cellular immune responses are antigen-specific immune responses mediated directly by activated immune cells rather than by the production of antibodies.** The distinction between humoral and cellular responses is historical and originates from the experimental observation that humoral immune function can be transferred by serum, whereas cellular immune function requires the transfer of cells. Most immune responses include both humoral and cellular components. Several types of cells, including cells from both the myeloid and lymphoid lineages, make up the immune system. Specific humoral and cellular immune responses to foreign antigens involve the coordinated action of populations of lymphocytes operating in concert with each other and with phagocytic cells (macrophages). These cellular interactions include both direct cognate interactions involving cell-to-cell contact and cellular interactions involving the secretion of and response to cytokines or lymphokines. Lymphoid cells are found in lymphoid tissues, such as lymph nodes or spleen, or in the peripheral circulation. The cells that make up the immune system originate from stem cells

in the bone marrow.

B Cells, Hormonal Immunity, and Monoclonal Antibodies

B lymphocytes synthesize and secrete antibodies. Mature, antigen-responsive B cells develop from pre-B cells (committed B-cell progenitors) and differentiate to become plasma cells, which produce large quantities of antibodies. Pre-B cells originate from bone marrow stem cells in adults after rearrangement of immunoglobulin genes from their germ-cell configuration. Mature B cells express cell surface immunoglobulin molecules that function as receptors for antigen.

Upon interaction with antigen, mature B cells respond to become antibody-producing cells. The process also requires the presence of appropriate cell–cell stimulatory signals and cytokines. Monoclonal antibodies are directed against a specific antigenic determinant. In contrast, polyclonal antibodies detect multiple epitopes that might be presented by just one or a panel of proteins. The *in vitro* production of monoclonal antibodies, pioneered by Kohler and Milstein in the 1970s, has become an invaluable diagnostic and therapeutic tool, particularly for the management of malignancies (61). The tumor antigen CA125, for example, was detected in a screen of antibodies generated against ovarian cancer cell lines. A radioimmunoassay is widely used to measure CA125 in the serum of patients with ovarian cancer and guide treatment decisions. Therapeutic approaches have utilized immunotoxin-conjugated monoclonal antibodies directed to human ovarian adenocarcinoma antigens. These antibodies induce tumor cell killing and can prolong survival in mice implanted with a human ovarian cancer cell line. However, many obstacles limit the clinical use of monoclonal antibodies, including tumor cell antigenic heterogeneity, modulation of tumor-associated antigens, and cross-reactivity of normal host and tumor-associated antigens. No unique tumor-specific antigens have been identified. All tumor antigens have to be considered as tumor-related antigens because they are expressed on the malignant as well as the nonmalignant tissues. Because most monoclonal antibodies are murine, the host's immune system can recognize and respond to these foreign mouse proteins. The use of the genetically engineered monoclonal antibodies composed of

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human-constant regions with specific antigen-reactive murine variable regions should result in reduced antigenicity to the host.

T Lymphocytes and Cellular Immunity

T lymphocytes have a central role in the generation of immune responses by acting as helper cells in both humoral and cellular immune responses and by acting as effector cells in cellular responses. T-cell precursors originate in bone marrow and move to the thymus, where they mature into functional T cells. During their thymic maturation, T cells learn to recognize antigen in the context of the *major histocompatibility complex (MHC)* type of the individual person. Self-responding T cells also are removed during development in the thymus (60).

T cells can be distinguished from other types of lymphocytes by their cell surface phenotype, based on the pattern of expression of various molecules, as well as by differences in their biologic functions. All mature T cells express certain cell surface molecules, such as the cluster determinant 3 (CD3) molecular complex and the T-cell antigen receptor, which is found in close association with the CD3 complex. **T cells recognize antigen through the cell surface T-cell antigen receptor (TCR).** The structure and organization of this molecule are similar to those of antibody molecules, which are the B-cell receptors for antigen. During T-cell development, the T-cell receptor gene undergoes

gene arrangements similar to those seen in B cells, but there are important differences between the antigen receptors on B cells and T cells. The T-cell receptor is not secreted, and its structure is somewhat different from that of antibody molecules. The way in which the B-cell and T-cell receptors interact with antigens is also quite different. T cells can respond to antigens only when these antigens are presented in association with MHC molecules on antigen-presenting cells. Effective antigen presentation involves the processing of antigen into small fragments of peptide within the antigen-presenting cell and the subsequent presentation of these fragments of antigen in association with MHC molecules expressed on the surface of the antigen-presenting cell. T cells can respond to antigen only when presented in this manner, unlike B cells, which can bind antigen directly, without processing and presentation by antigen-presenting cells (60).

There are two major subsets of mature T cells that are phenotypically and functionally distinct: *T helper/inducer cells*, which express the CD4 cell surface marker, and the *T suppressor/cytotoxic cells*, which express the CD8 marker.

The expression of these markers is acquired during the passage of T cells through the thymus. CD4 T cells can provide help to B cells, resulting in the production of antibodies by B cells, and interact with antigen presented by antigen-presenting cells in association with MHC class II molecules. CD4 T cells can also act as helper cells for other T cells. CD8 T cells include cells that are cytotoxic (cells that can kill target cells bearing appropriate antigens), and they interact with antigen presented on target cells in association with MHC class I molecules. The CD8 T-cell subset also contains suppressor T cells. These T cells can inhibit the biologic functions of B cells or other T cells (60). Although the primary biologic role of *cytotoxic T cells (CTLs)* seems to be lysis of virus-infected autologous cells, cytotoxic immune T cells can mediate the lysis of tumor cells directly. Presumably, CTLs recognize antigens associated with MHC class I molecules on tumor cells through their antigen-specific T-cell receptor, setting off a series of events that ultimately results in the lysis of the target cell.

Monocytes and Macrophages

Monocytes and macrophages, which are myeloid cells, have important roles in both innate and adaptive immune responses; macrophages play a key part in the generation of immune responses. T cells do not respond to foreign antigens unless those antigens are processed and presented by antigen-presenting cells. **Macrophages (and B cells) express MHC class II molecules and are effective antigen-presenting cells for CD4 T cells.** Helper-inducer (CD4) T cells that bear a T-cell receptor of appropriate antigen and self-specificity

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are activated by this antigen-presenting cell to provide help (various factors—lymphokines—that induce the activation of other lymphocytes). In addition to their role as antigen-presenting cells, macrophages play an important part in innate responses by ingesting and killing microorganisms. Activated macrophages, in addition to their many other functional capabilities, can act as cytotoxic, antitumor killer cells.

Natural Killer Cells

Natural killer cells are effector cells in an innate type of immune response: the nonspecific killing of tumor cells and virus-infected cells. Therefore, **NK activity represents an innate form of immunity that does not require an adaptive, memory response for optimal biologic function, but the antitumor activity can be increased by exposure to several agents, particularly cytokines such as interleukin-2 (IL-2).** Characteristically, NK cells have a large granular lymphocyte morphology. NK cells display a pattern of cell surface markers that differs from those characteristic of T or B cells. NK cells can express a

receptor for the crystallizable fragment (Fc) portion of antibodies, as well as other NK-associated markers. Natural killer cells appear to be functionally and phenotypically heterogeneous, at least when compared with T or B cells. The cells that can carry out antibody-dependent cellular cytotoxicity, or antibody-targeted cytotoxicity, are NK-like cells. Antibody-dependent cellular cytotoxicity by NK-like cells has been shown to result in the lysis of tumor cells in vitro. The mechanisms of this tumor cell killing are not clearly understood, although close cellular contact between the effector cell and the target cell seems to be required.

Biologic Response Modifiers

Most immunotherapeutic agents used in the treatment of cancer have been nonspecific agents that, when introduced into the human system, elicit a generalized inflammatory reaction and immune response, probably mediated by the secretion of a range of cytokines by many different types of cells. These agents have diverse and broad biologic effects and are often referred to as immunomodulators or biologic response modifiers.

The response of a given patient to treatment with biologic response modifiers depends on the ability to react to treatment with a generalized immune response. It is possible that some elements of the immune response elicited by immunotherapeutic agents or biologic response modifiers may be counterproductive, possibly causing immune suppression, inducing the production of cytokines that enhance tumor growth or inducing an unfavorable or inappropriate immune response.

Bacille Calmette-Guérin (BCG) vaccine has been widely used in many tumor systems, either systemically, by injection into the lesion, or by scarification (62). Occasionally, it has been mixed with whole irradiated tumor cells and injected into the patient as a vaccine. In a large series, intracutaneous injection of melanoma lesions with BCG resulted in some tumor regression in patients with cutaneous recurrence, but visceral or parenchymal metastatic disease is resistant to this treatment. Although there have been some preliminary observations about the use of BCG as an adjuvant in children with acute lymphocytic leukemia and with stage II melanoma, randomized studies have not shown any appreciable responses.

Cytokines, Lymphokines, and Immune Mediators

Many events in the generation of immune responses (as well as during the effector phase of immune responses) require or are enhanced by cytokines, which are soluble mediator molecules (Table

6.5) (63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82). Cytokines are pleiotropic in that they have multiple biologic functions that depend on the type of target cell or its maturational state. Cytokines are also heterogeneous in the sense that most cytokines share little structural or amino acid homology. ***Cytokines are called monokines if they are derived from monocytes, lymphokines if they are derived from lymphocytes, interleukins if they exert***

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their actions on leukocytes, or interferons (IFNs) if they have antiviral effects. They are produced by a wide variety of cell types and seem to have important roles in many biologic responses outside the immune response, such as inflammation or hematopoiesis. They may also be involved in the pathophysiology of a wide range of diseases and show great potential as therapeutic agents in immunotherapy for cancer. Although cytokines are a heterogeneous group of proteins, they share some characteristics. For instance, most cytokines are low-to intermediate-molecular-weight (10–60 kd) glycosylated secreted proteins. They are also

involved in immunity and inflammation, are produced transiently and locally (they act in an autocrine and paracrine rather than an endocrine manner), are extremely potent in small concentrations, and interact with high-affinity cellular receptors that are specific for each cytokine. The cell surface binding of cytokines by specific receptors results in signal transduction followed by changes in gene expression and, ultimately, by changes in cellular proliferation or altered cell behavior, or both. Their biologic actions overlap, and exposure of responsive cells to multiple cytokines can result in synergistic or antagonistic biologic effects.

Interleukins

The interleukins represent a family of molecules that play a major role in immune responses (Table 6.5).

Interleukin-1

Interleukin-1 has a wide range of biologic activities, including direct effects on several cells involved in immune responses (63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82). It is involved in fever and inflammatory responses and may play a role in the pathogenesis of several diseases, such as rheumatoid arthritis. There are two defined forms of IL-1, IL-1 α and IL-1 β , which have similar biologic activities. Interleukin-1 can be released as a soluble form or can be found as a cell-associated molecule on the cell surface of macrophages. The primary sources of IL-1 are macrophages, the phagocytic cells of the liver and spleen, some B cells, epithelial cells, certain brain cells, and the cells lining the synovial spaces. Interleukin-1 has a broad range of target cells and biologic activities, as do most lymphokines. A principal role of IL-1 is in the initiation of early events in immune responses (62,68).

Interleukin-2

Interleukin-2 is a lymphokine that was originally called *T-cell growth factor*, which indicates one of the major biologic activities of this molecule. Failure of T cells to produce IL-2 results in the absence of a T-cell immune response and a diminution of the antibody response. Natural human IL-2 is a 15-kd glycoprotein and is produced primarily by activated T cells. For IL-2 to exert its proliferation-inducing effects, it has to interact with a specific receptor for IL-2 on the surface of the target cell. The high-affinity receptor for IL-2 consists of two polypeptides, the α (75 kd) and β (55 kd) chains. After activation, T cells express greatly increased numbers of this high-affinity receptor for IL-2 and respond to IL-2 with increased proliferation. Stimulation of resting T cells with antigen presented in the context of self (antigen associated with an MHC molecule on the surface of an antigen-presenting cell) and with IL-1, therefore, induces synthesis and secretion of IL-2. During this activation process, responding T cells undergo an alteration in their cell surface receptors, including the expression of cell surface receptors for IL-2. Continuing exposure to IL-2 leads to the proliferation of T cells bearing the IL-2 receptor, thereby serving as an activation and response-amplification stage in the generation of immune responses. Activated T cells not only respond to IL-2 but also produce IL-2. Interleukin-2 can, therefore, act in an autocrine manner (the cells producing the lymphokine then respond to it) or in a paracrine fashion (the IL-2 produced by a T cell is taken up and responded to by neighboring cells). Since its original description as a T-cell growth hormone, IL-2 has been shown to have various other immune functions, including the promotion of B-cell activation and maturation and activation of monocytes and NK cells. Interleukin-2 can also lead directly or indirectly to the stimulation of the production of interferon and other cytokines.

Table 6.5 Sources, Target Cells, and Biological Activities of Cytokines Involved			
Cytokine	Cellular Source	Target Cells	Biologic Effects
IL-1	Monocytes and macrophages	T cells, B cells Neurons	Costimulator Pyrogen
IL-2	Tumor cells T cells (T _H 1)	Endothelial cells T cells	Growth
		B cells	Activation and antibody production
		NK cells	Activation and growth
IL-3	T cells	Immature hemopoietic stem cells	Growth and differentiation
IL-4	T cells (T _H 2)	B cells	Activation and growth; isotype switch to IgE; increased MHCII expression
		T cells	Growth
IL-6	Monocytes and macrophages	B cells	Differentiation, antibody production
	T cells, B cells	T cells	Costimulator
	Ovarian cancer cells	Hepatocytes	Induction of acute-phase response
	Other tumors Tumor cells	Stem cells Autocrine/paracrine growth and viability-enhancing factor	Growth and differentiation
IL-10	T cells (T _H 2)	T cells (T _H 1)	Inhibition of cytokine synthesis
	Monocytes and macrophages	Monocytes and macrophages	Inhibition of Ag presentation and cytokine production
		B cells	Activation
IL-12	Monocytes	NK cells, T cells (T _H 1)	Induction
IL-13	T cells (T _H 2), mast cells, NK cells	B cells, T _H 2 cells, macrophages	Regulates IgE secretion by B cell T _H 2 development Macrophage activity
IL-15	Dendritic cells, monocytes, placenta, kidney, lung, heart, T cells	Mast cells	NK cell development and function Mast cell proliferation
IL-16	CD4+ and CD8+ T cells, eosinophils, mast cells, dendritic cells	T cells, monocytes, dendritic cells, eosinophils	Prevent antigen-induced T-cell death, chemotactic factor for CD4 + T cells, monocytes, eosinophils, dendritic cells
IL-17	Activated CD4 + T cells	T cells, fibroblasts	T-cell activation Induces secretion of cytokines by fibroblasts
IL-27	Monocytes, macrophages	CD4 + T cells	Proliferation of naïve CD4 + T cells, synergizes with IL-12
IFN-γ	T cells (T _H 1)	Monocytes/ macrophages	Activation
	NK cells	NK cells, T cells, B cells	Activation Enhances responses

TNF- α	Monocytes and macrophages T cells Monokine production Costimulator Pyrogen	Monocytes/ macrophages T cells, B cells Neurons	Endothelial cells Muscle and fat cells	Activation, inflammation Catabolism/cachexia
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IL-1, interleukin-1; T_H1, type 1 T helper lymphocyte; NK cells, natural killer cells; T_H2, type 2 T helper lymphocyte; IgE, immunoglobulin E; MHCII, major histocompatibility complex class II; Ag, antigen; IFN, interferon; TNF, tumor necrosis factor. Modified from **Berek JS, Martinez-Maza O**. Immunology and immunotherapy. In: **Lawton FG, Neijt JP, Swenerton KD**. *Epithelial cancer of the ovary*. London, England: BMJ, 1995:224, with permission.

Interleukin-3

Interleukin-3, a factor that can increase the early differentiation of hematopoietic cells (82), may find a role in immunotherapy because of its ability to induce hematopoietic differentiation in people undergoing aggressive chemotherapeutic treatment or bone marrow transplantation.

Interleukin-4, Interleukin-5, and Interleukin-6

B-lymphocyte activation and differentiation to immunoglobulin-secreting plasma cells are promoted by cytokines produced by helper T lymphocytes or monocytes (Table 6.5) (55,56). Several cytokines originally described as B-cell stimulating factors (IL-4, IL-5, and IL-6) have additional biologic activities. For instance, IL-6 (a factor that can induce B-lymphocyte differentiation to immunoglobulin-secreting cells) is a pleiotropic cytokine with biologic activities that include the induction of cytotoxic T-lymphocyte differentiation, the induction of acute-phase reactant production by hepatocytes, and activity as a colony-stimulating factor for hematopoietic stem cell (64). Interleukin-6 is produced primarily by activated monocyte-macrophages and T lymphocytes. Interestingly, several types of tumor cells produce IL-6, and it has been proposed as an autocrine-paracrine growth factor in different types of neoplasms (64,65,66,67,68,69). It may prove to be an effective antitumor agent by virtue of its ability to enhance antitumor T-cell-mediated immune responsiveness (69,70).

Interleukin-8 and Interleukin-10

Interleukin-10, a 35- to 40-kd cytokine, is also called *cytokine synthesis inhibitory factor* because of its activity as an inhibitor of cytokine production. It is produced by a subset of CD4 cells, type 2 (T_H2) cells, and inhibits the cytokine production by another CD4 cell subset, type 1 (T_H1) cells (71). **T_H1 and T_H2 are two helper T-cell subpopulations that control the nature of an immune response by secreting a characteristic and mutually antagonistic set of cytokines: Clones of T_H1 produce IL-2 and interferon- γ (IFN- γ), whereas T_H2 clones produce IL-4, IL-5, IL-6, and IL-10 (72).** A similar dichotomy between T_H1- and T_H2-type responses has been reported in humans (73,74). Human IL-10 inhibits the production of IFN- γ and other cytokines by human peripheral blood mononuclear cells (75) and by suppressing the

release of cytokines (IL-1, IL-6, IL-8, and TNF- α) by activated monocytes (76,77,78). Interleukin-

10 also downregulates class II MHC expression on monocytes, resulting in a strong reduction in the antigen-presenting capacity of these cells (78). Together, these observations support the concept that IL-10 has an important role as an immune-inhibitory cytokine.

Because epithelial cancers of the ovary usually remain confined to the peritoneal cavity, even in the advanced stages of the disease, it has been suggested that the growth of ovarian cancer intraperitoneally could be related to a local deficiency of antitumor immune effector mechanisms (79). Studies have shown that ascitic fluid from patients with ovarian cancer contained increased concentrations of IL-10 (80). Various other cytokines are also seen in ascitic fluid obtained from women with ovarian cancer including IL-6, IL-10, TNF- α , *granulocyte colony-stimulating factor (G-CSF)*, and *granulocyte-macrophage colony-stimulating factor (GM-CSF)* (81). A similar pattern was seen in serum samples from women with ovarian cancer with elevations of IL-6 and IL-10.

Tumor necrosis factor- α is a cytokine that can be directly cytotoxic for tumor cells, can increase immune cell-mediated cellular cytotoxicity, and can activate macrophages and induce secretion of monokines. Other biologic activities of TNF- α include the induction of cachexia, inflammation, and fever; it is an important mediator of endotoxic shock.

Interferons

There are three types of interferons: IFN- α , IFN- β , and IFN- γ (54,55,83). They can interfere with viral production in infected cells and have various effects on the immune system as well as direct antitumor effects. For instance, **IFN- γ , a cytokine produced by T lymphocytes, can affect immune function by increasing the induction of MHC molecule expression, increasing the activity of antigen-presenting cells, and thereby increasing T-lymphocyte activation.**

Cytokines in Cancer Therapy

Cytokines are extraordinarily pleiotropic with a bewildering array of biologic activities, including some outside the immune system (54,55,63,69). Because some cytokines have direct or indirect antitumor and immune-enhancing effects, several of these factors have been used in the experimental treatment of cancer.

The precise roles of cytokines in antitumor responses have not been elucidated.

Cytokines can exert antitumor effects by many different direct or indirect activities. It is possible that a single cytokine could increase tumor growth directly by acting as a growth factor while at the same time increasing immune responses directed toward the tumor. The potential of cytokines to increase antitumor immune responses has been tested in experimental adoptive immunotherapy by exposing the patient's peripheral blood cells or tumor-infiltrating lymphocytes to cytokines such as IL-2 *in vitro*, thus generating activated cells with antitumor effects that can be given back to the patient (84,85,86). Some cytokines can also exert direct antitumor effects. Tumor necrosis factor can induce cell death in sensitive tumor cells.

The effects of cytokines on patients with cancer might be modulated by soluble receptors or blocking factors. For instance, blocking factors for TNF and for lymphotoxin were found in ascitic fluid from patients with ovarian cancer (87). Such factors could inhibit the cytolytic effects of TNF or lymphotoxin and should be taken into account in the design of clinical trials of intraperitoneal infusion of these cytokines.

Cytokines have growth-increasing effects on tumor cells in addition to inducing antitumor effects. They can act as autocrine or paracrine growth factors for human tumor cells,

including those of nonlymphoid origin. For instance, IL-6 (which is produced by various types of human tumor cells) can act as a growth factor for human myeloma, Kaposi's sarcoma, renal carcinoma, and epithelial ovarian cancer cells (63,64,65,66,67,68,69).

Clearly, cytokines are of great potential value in the treatment of cancer, but because of their multiple—even conflicting—biologic effects, a thorough understanding of cytokine biology is essential for their successful use (83,84,85,86,87,88,89,90,91).

Adoptive Immunotherapy

The *ex vivo* enhancement of antitumor immune cell responses, including the generation of lymphokine-activated killer (LAK) cells or the activation of tumor-infiltrating lymphocytes (TIL), has provided new immune system-based approaches for antitumor responses. The simultaneous treatment of patients with *ex vivo*-activated autologous cells, along with IL-2, is the basis of adoptive immunotherapy, a form of experimental antitumor immunotherapy. In particular, adoptive immunotherapy with IL-2 can produce regression of tumor in various animals and human tumors, such as melanoma and renal cell carcinoma, when used in conjunction with the adoptive transfer of autologous LAK cells (84,85).

Exposure of peripheral blood mononuclear cells to cytokines *in vitro* (particularly IL-2) leads to the generation of cytotoxic effect cells called *LAK cells* (85). These cells are cytotoxic for various tumor cells, including those that are resistant to NK-cell- or T-cell-mediated lysis. Experimental treatment of human subjects with autologous *ex vivo*-generated LAK cells and IL-2 has yielded tumor regression in some cases (84,85,86,87,88). This treatment has resulted in some complete responses (86); the combined response rate was 27% in 146 patients with cancer who were treated in two separate studies (88,89,90). The overall response rate to LAK treatment is low, however, and this type of adoptive immunotherapy causes high morbidity (90). It is also costly and impractical in most medical settings.

Much current experimental work is aimed at developing more efficient and practical applications of adoptive immunotherapy (91,92,93,94,95,96,97). One approach involves the *ex vivo* generation of immune effector cells from TILs and dendritic cells, which are lymphocytes that are isolated from tumors and activated and expanded *in vitro* by exposure to IL-2. These cells can be administered to the patient with IL-2 (91,92). This approach is hampered by the need to expand a limited number of TILs *in vitro* to generate enough effector cells for treatment. Recently, attention has been directed toward the development of new methods for the generation of LAK cells or TILs, including methods that use cytokines other than IL-2 to stimulate these cells. Another approach that has been explored in animal studies involves the targeting of activated T lymphocytes with a bifunctional monoclonal antibody that binds to the CD3-T-cell receptor complex (on the target tumor cell) (93). This approach has the potential advantage of allowing a large number of the activated lymphocytes to target their effects directly on tumor cells, thereby reducing the need to amplify a large number of effector cells from TILs. It also has the potential to avoid some of the side effects associated with LAK treatment, which is a more nonspecific form of adoptive immunotherapy.

Factors That Trigger Neoplasia

Cell biology is characterized by considerable redundancy and functional overlap, so that a defect in one mechanism does not invariably jeopardize the function of the cell. However, when a sufficient number of abnormalities in structure and function occur, normal cell function is jeopardized, and uncontrolled cell growth or cell death results. Either endpoint may result from accumulated genetic mutations over time. Factors have been identified that enhance the likelihood of genetic mutations, jeopardize normal cell biology, and may increase the risk

of cancer.

Increased Age

Increasing age is considered the single most important risk factor for the development of cancer (98). Cancer is diagnosed in as much as 50% of the population by 75 years of age (99). It has been suggested that the increasing risk of cancer with age reflects the accumulation of critical genetic mutations over time, which ultimately culminates in neoplastic transformation. The basic premise of the multistep somatic mutation theory of carcinogenesis is that genetic or epigenetic alterations of numerous independent genes results in cancer. Factors that have been associated with an increased likelihood of cancer include exposure to exogenous mutagens, altered host immune function, and certain inherited genetic syndromes and disorders.

Environmental Factors

A mutagen is a compound that results in a genetic mutation. A number of environmental pollutants act as mutagens when tested *in vitro*. Environmental mutagens usually produce specific types of mutations that can be differentiated from spontaneous mutations. As an example, activated hydrocarbons tend to produce GT transversions (100). A carcinogen is a compound that can produce cancer. It is important to recognize that all carcinogens are not mutagens and that all mutagens are not necessarily carcinogens.

Smoking

Cigarette smoking is perhaps the best known example of mutagen exposure that is associated with the development of lung cancer when the exposure is of sufficient duration and quantity in a susceptible individual. An association between cigarette smoking and cervical cancer has been recognized for decades. More recently, **it has been determined that the mutagens in cigarette smoke are selectively concentrated in cervical mucus** (52). It has been hypothesized that exposure of the proliferating epithelial cells of the transformation zone to cigarette smoke mutagens may increase the likelihood of DNA damage and subsequent cellular transformation.

Others have observed that human papillomavirus DNA is frequently inserted into the fragile histidine triad gene (FHIT) in cervical cancer specimens. The FHIT is an important tumor suppressor gene. Cigarette smoking might facilitate the incorporation of HPV DNA into the FHIT gene with subsequent disruption of correct tumor suppressor gene function.

Radiation

Radiation exposure can increase the risk of cancer. The overall risk of radiation-induced cancer is approximately 10% greater in women than in men (101). This difference has been attributed to gender-specific cancers, including breast cancer. Radiation-induced cancer may be the result of sublethal DNA damage that is not repaired (101). Normally, radiation damage prompts an S-phase arrest so that DNA damage is repaired. This requires normal *p53* gene function. If DNA repair fails, the damaged DNA is propagated to daughter cells following mitosis. If a sufficient number of critical genes are mutated, cellular transformation may result.

Immune Function

Systemic immune dysfunction has been recognized as a risk factor for cancer for decades. The immunosuppressed renal transplant patient may have a 40-fold increased risk of cervical cancer (52). Patients infected with human immunodeficiency virus (HIV) who have a depressed CD4 cell count have been reported to be at increased risk of cervical dysplasia and invasive disease (96). Individuals who have undergone high-dose chemotherapy with stem cell support may be at increased risk of developing a variety of solid neoplasms. These examples illustrate the importance of immune function in host

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surveillance for transformed cells. Another example of altered immune function that may be related to the development of cervical dysplasia is the alteration in mucosal immune function that occurs in women who smoke cigarettes (52). The Langerhans cell population of the cervix is decreased in women who smoke. Langerhans cells are responsible for antigen processing. It is postulated that a reduction in these cells increases the likelihood of successful human papillomavirus infection of the cervix.

Diet

The role of diet in disease prevention and predisposition is widely recognized but poorly understood (96,99). Dietary fat intake has been correlated with the risk of colon and breast cancer. Fiber is considered protective against colon cancer. With respect to the female reproductive system, epidemiologic studies provide conflicting results. Deficiencies of folic acid and vitamins A and C have been associated with the development of cervical dysplasia and cervical cancer. Considerable research must be performed to clarify the impact of diet on cancer prevention and development.

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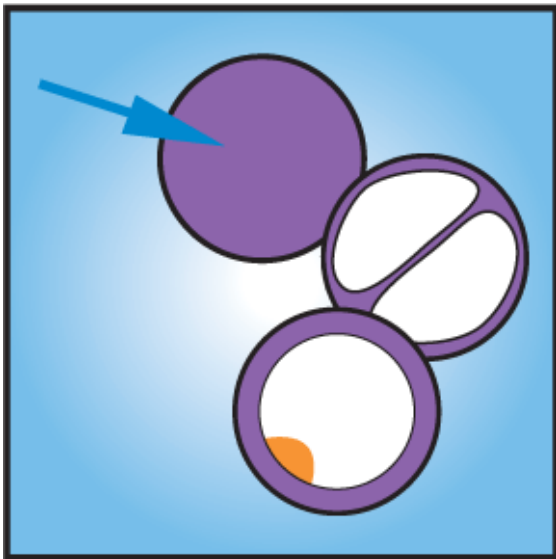
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7

Reproductive Physiology

David L. Olive

Steven F. Palter



- **The female reproductive process involves the central nervous system (primarily hypothalamus), the pituitary gland, the ovary, and the uterus (endometrium). All must function appropriately for normal reproduction to occur.**
- **Hypothalamic gonadotropin-releasing hormone (GnRH) simultaneously regulates both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the pituitary, and does so by being secreted in a pulsatile manner. The pulse frequency determines the relative amounts of LH and FSH secretion.**
- **The ovary responds to FSH and LH in a defined, sequential manner to produce follicular growth, ovulation, and corpus luteum formation. The cycle is designed to produce an optimal environment for pregnancy; should this not occur, the cycle begins again.**
- **The ovary produces estrogen in the early menstrual cycle, which is responsible for endometrial growth. Following ovulation, progesterone is also produced**

in significant quantities, which transforms the endometrium to a form ideal for implantation of the embryo. If no pregnancy occurs, the ovary ceases to produce estrogen and progesterone, the endometrium is sloughed, and the cycle begins again.

The reproductive process in women is a complex and highly evolved interaction of many components. The carefully orchestrated series of events that contributes to a normal ovulatory menstrual cycle requires precise timing and regulation of hormonal input from the central nervous system, the pituitary gland, and the ovary. This delicately balanced process can be easily disrupted and result in reproductive failure, which is a major clinical issue confronting gynecologists. To effectively manage such conditions, it is critical that gynecologists understand the normal physiology of the menstrual cycle. The anatomic structures, hormonal components, and interactions between the two play a vital role in the function of the reproductive system. Fitting together the various pieces of this intricate puzzle will provide "the big picture": an overview of how the reproductive system of women is designed to function.

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Neuroendocrinology

Neuroendocrinology represents facets of two traditional fields of medicine: endocrinology, which is the study of hormones (i.e., substances secreted into the bloodstream that have diverse actions at sites remote from the point of secretion), and neuroscience, which is the study of the action of neurons. The discovery of neurons that transmit impulses and secrete their products into the vascular system to function as hormones themselves, a process known as neurosecretion, demonstrates that the two systems are intimately linked. For instance, the menstrual cycle is regulated through the feedback of hormones on the neural tissue of the central nervous system (CNS).

Anatomy

Hypothalamus

The hypothalamus is a small neural structure situated at the base of the brain above the optic chiasm and below the third ventricle (Fig. 7.1). It is connected directly to the pituitary gland and is the part of the brain that is the source of many pituitary secretions. Anatomically, the hypothalamus is divided into three zones: *periventricular* (adjacent to the third ventricle), *medial* (primarily cell bodies), and *lateral* (primarily axonal). Each zone is further subdivided into structures known as nuclei, which represent locations of concentrations of similar types of neuronal cell bodies (Fig. 7.2).

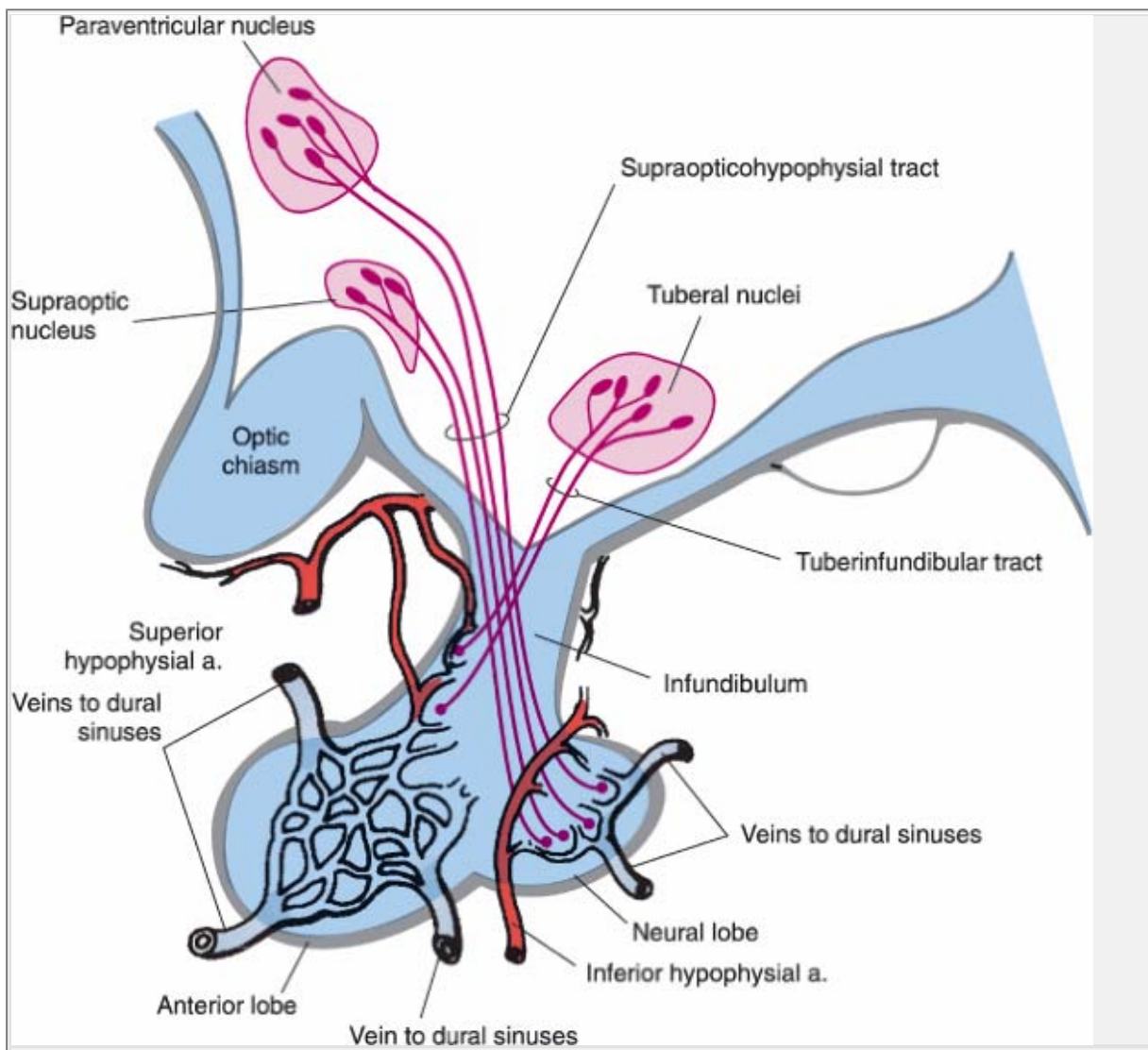


Figure 7.1 The hypothalamus and its neurologic connections to the pituitary.

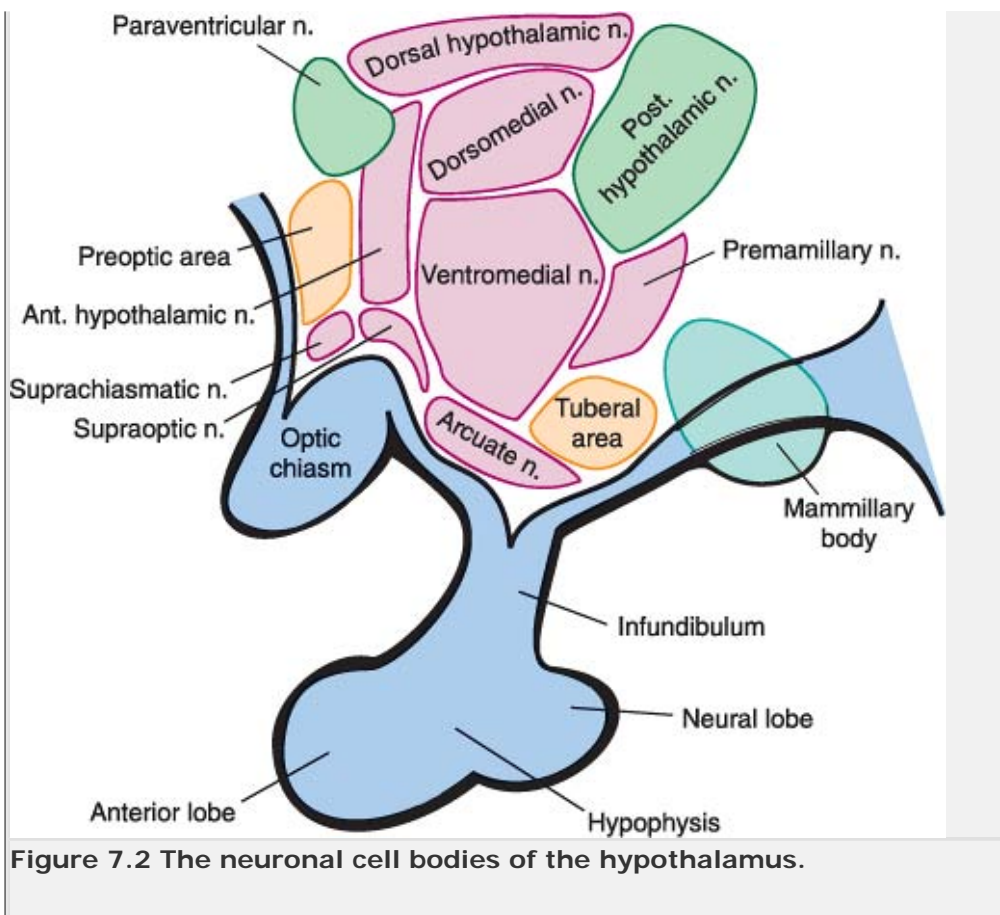


Figure 7.2 The neuronal cell bodies of the hypothalamus.

The hypothalamus is not an isolated structure within the CNS; instead, it has multiple interconnections with other regions in the brain. In addition to the well-known pathways of hypothalamic output to the pituitary, there are numerous less well-characterized pathways of output to diverse regions of the brain, including the limbic system (amygdala and hippocampus), the thalamus, and the pons (1). Many of these pathways form feedback loops to areas supplying neural input to the hypothalamus.

Several levels of feedback to the hypothalamus exist and are known as the long, short, and ultrashort feedback loops. The long feedback loop is composed of endocrine input from circulating hormones, just as feedback of androgens and estrogens onto steroid receptors is present in the hypothalamus (2,3). Similarly, pituitary hormones may feed back to the hypothalamus and serve important regulatory functions in short-loop feedback. Finally, hypothalamic secretions may directly feed back to the hypothalamus itself in an ultrashort feedback loop.

The major secretory products of the hypothalamus are the pituitary-releasing factors (Fig. 7.3):

- *Gonadotropin-releasing hormone (GnRH)*, which controls the secretion of *luteinizing hormone (LH)* and *follicle-stimulating hormone (FSH)*
- *Corticotropin-releasing hormone (CRH)*, which controls the release of *adrenocorticotrophic hormone (ACTH)*
- *Growth hormone-releasing hormone (GHRH)*, which regulates the release of *growth hormone (GH)*

Thyrotropin-releasing hormone (TRH), which regulates the secretion of thyroid-stimulating hormone (TSH)

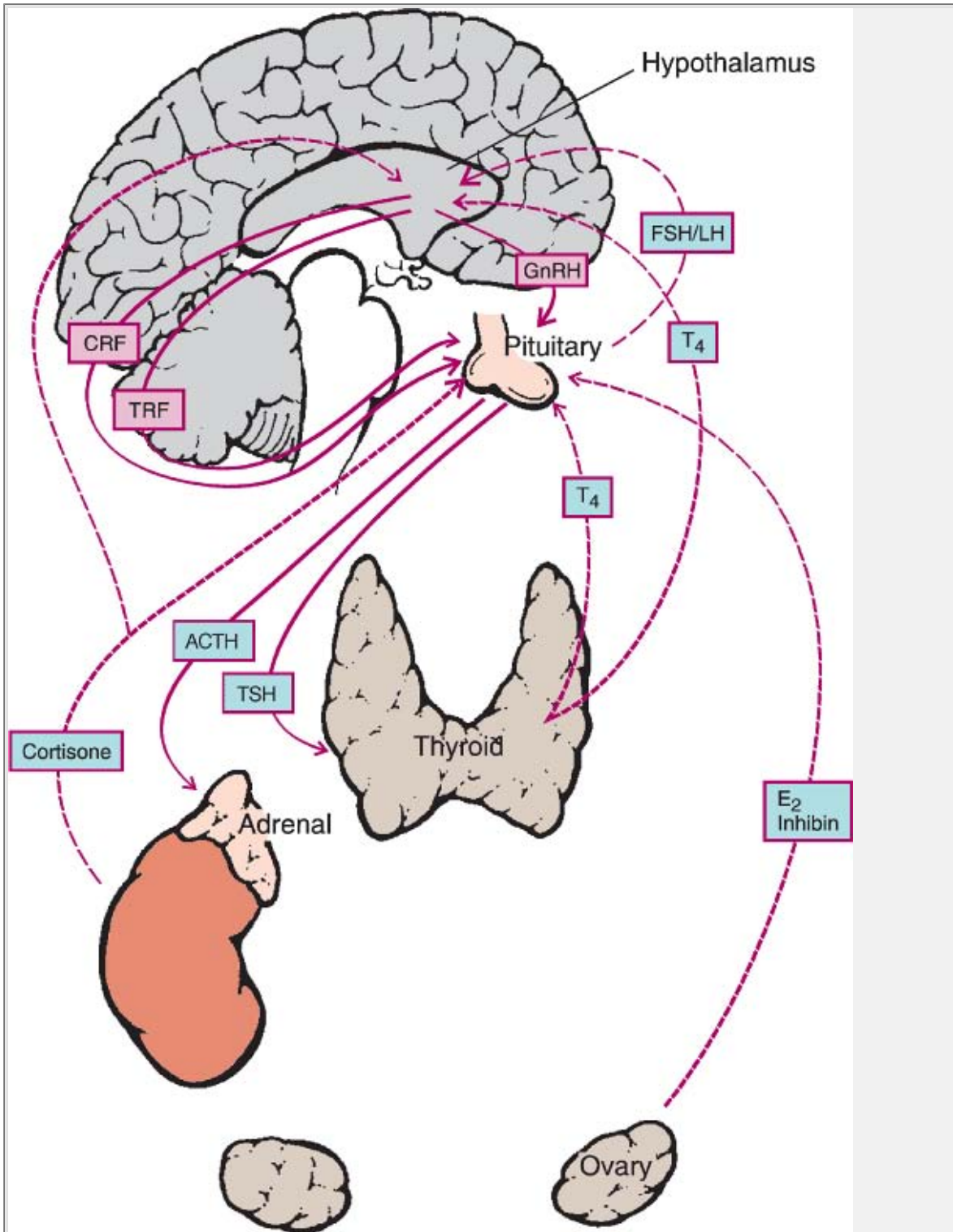


Figure 7.3 The hypothalamic secretory products function as pituitary-releasing factors that control the endocrine function of the ovaries, the thyroid, and the adrenal glands.

The hypothalamus is the source of all neurohypophyseal hormone production. The neural posterior pituitary can be viewed as a direct extension of the hypothalamus connected by the fingerlike infundibular stalk. The discovery that the capillaries in the median eminence differ from those in other regions of the brain was a major one. Unlike the usual tight junctions that exist between adjacent capillary endothelial lining cells, the capillaries in this region are fenestrated in the same manner as capillaries outside the CNS. As a result, there is no blood–brain barrier in the median eminence.

Pituitary

The pituitary is divided into three regions or lobes: anterior, intermediate, and posterior. The anterior pituitary (adenohypophysis) is quite different structurally from the posterior neural pituitary (neurohypophysis), which is a direct physical extension of

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the hypothalamus. The adenohypophysis is derived embryologically from epidermal ectoderm from an infolding of Rathke's pouch. Therefore, it is not composed of neural tissue, as is the posterior pituitary, and does not have direct neural connections to the hypothalamus. Instead, a unique anatomic relationship exists that combines elements of neural production and endocrine secretion. The adenohypophysis itself has no direct arterial blood supply. Its major source of blood flow is also its source of hypothalamic input—the portal vessels. Blood flow in these portal vessels is primarily from the hypothalamus to the pituitary. Blood is supplied to the posterior pituitary via the superior, middle, and inferior hypophyseal arteries. In contrast, the anterior pituitary has no direct arterial blood supply. Instead, it receives blood via a rich capillary plexus of the portal vessels that originate in the median eminence of the hypothalamus and descend along the pituitary stalk. This pattern is not absolute, however, and retrograde blood flow has occurred (4). This blood flow, combined with the location of the median eminence outside the blood–brain barrier, permits bidirectional feedback control between the two structures.

The specific secretory cells of the anterior pituitary have been classified based on their hematoxylin- and eosin-staining patterns. Acidophilic-staining cells primarily secrete GH and prolactin and, to a variable degree, ACTH (5). The gonadotropins are secreted by basophilic cells, and TSH is secreted by the neutral-staining chromophobes.

Reproductive Hormones

Hypothalamus

Gonadotropin-releasing Hormone

Gonadotropin-releasing hormone (GnRH) (also called luteinizing hormone–releasing hormone, or LHRH) is the controlling factor for gonadotropin secretion (6). It is a decapeptide produced by neurons with cell bodies primarily in the arcuate nucleus of the hypothalamus (7,8,9) (Fig. 7.4). Embryologically, these neurons originate in the olfactory pit and then migrate to their adult locations (10). These GnRH-secreting neurons project axons that terminate on the portal vessels at the median eminence where GnRH is secreted for delivery to the anterior pituitary. Less clear in function are multiple other secondary projections of GnRH neurons to locations within the CNS.

The gene that encodes GnRH produces a 92 amino acid precursor protein, which contains not only the GnRH decapeptide but also a 56 amino acid peptide known as GnRH-associated peptide,

or GAP. The GnRH-associated peptide is a potent inhibitor of prolactin secretion as well as a stimulator of gonadotropin release.

Pulsatile Secretion

Gonadotropin-releasing hormone is unique among releasing hormones in that it simultaneously regulates the secretion of two hormones—FSH and LH. It also is unique among the body's hormones because it must be secreted in a pulsatile fashion to be effective, and the pulsatile release of GnRH influences the release of the two gonadotropins (11,12,13). Using animals that had undergone electrical destruction of the arcuate nucleus and had no detectable levels of gonadotropins, a series of experiments were performed with varying dosages and intervals of GnRH infusion (13,14). Continual infusions did not result in gonadotropin secretion, whereas a pulsatile pattern led to physiologic secretion patterns and follicular growth. Continual exposure of the pituitary gonadotroph to GnRH results in a phenomenon called *downregulation*, through which the number of gonadotroph cell surface GnRH receptors is decreased (15). Similarly, intermittent exposure to GnRH will "upregulate" or "autoprime" the gonadotroph to increase its number of GnRH receptors (16). This allows the cell to have a greater response to subsequent GnRH exposure. Similar to the intrinsic electrical pacemaker cells of the heart, this action most likely represents an intrinsic property of the GnRH-secreting neuron, although it is subject to modulation by various neuronal and hormonal inputs to the hypothalamus.

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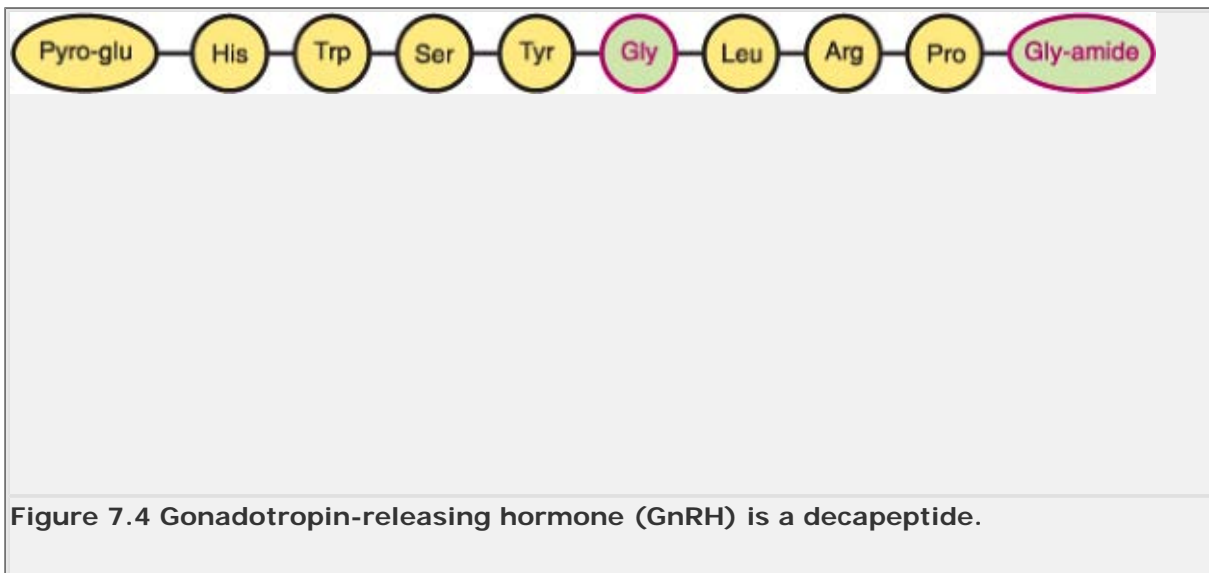


Figure 7.4 Gonadotropin-releasing hormone (GnRH) is a decapeptide.

The continual pulsatile secretion of GnRH is necessary because GnRH has an extremely short half-life (only 2–4 minutes) as a result of rapid proteolytic cleavage.

The pulsatile secretion of GnRH varies in both frequency and amplitude throughout the menstrual cycle and is tightly regulated (17,18) (Fig. 7.5). The follicular phase is characterized by frequent, small-amplitude pulses of GnRH secretion. In the late follicular phase, there is an increase in both frequency and amplitude of pulses. During the luteal phase, however, there is a progressive lengthening of the interval between pulses. The amplitude in the luteal phase is higher than that in the follicular phase, but it declines progressively over the two weeks. This variation in pulse frequency allows for variation in both LH and FSH throughout the menstrual cycle. For example, decreasing the pulse frequency of GnRH decreases LH secretion but increases FSH, an important aspect of enhancing FSH availability in the late luteal phase. The pulse frequency is not the sole determinant of pituitary response, however; additional hormonal influences, such as those exerted by ovarian peptides and sex steroids, can modulate

the GnRH effect.

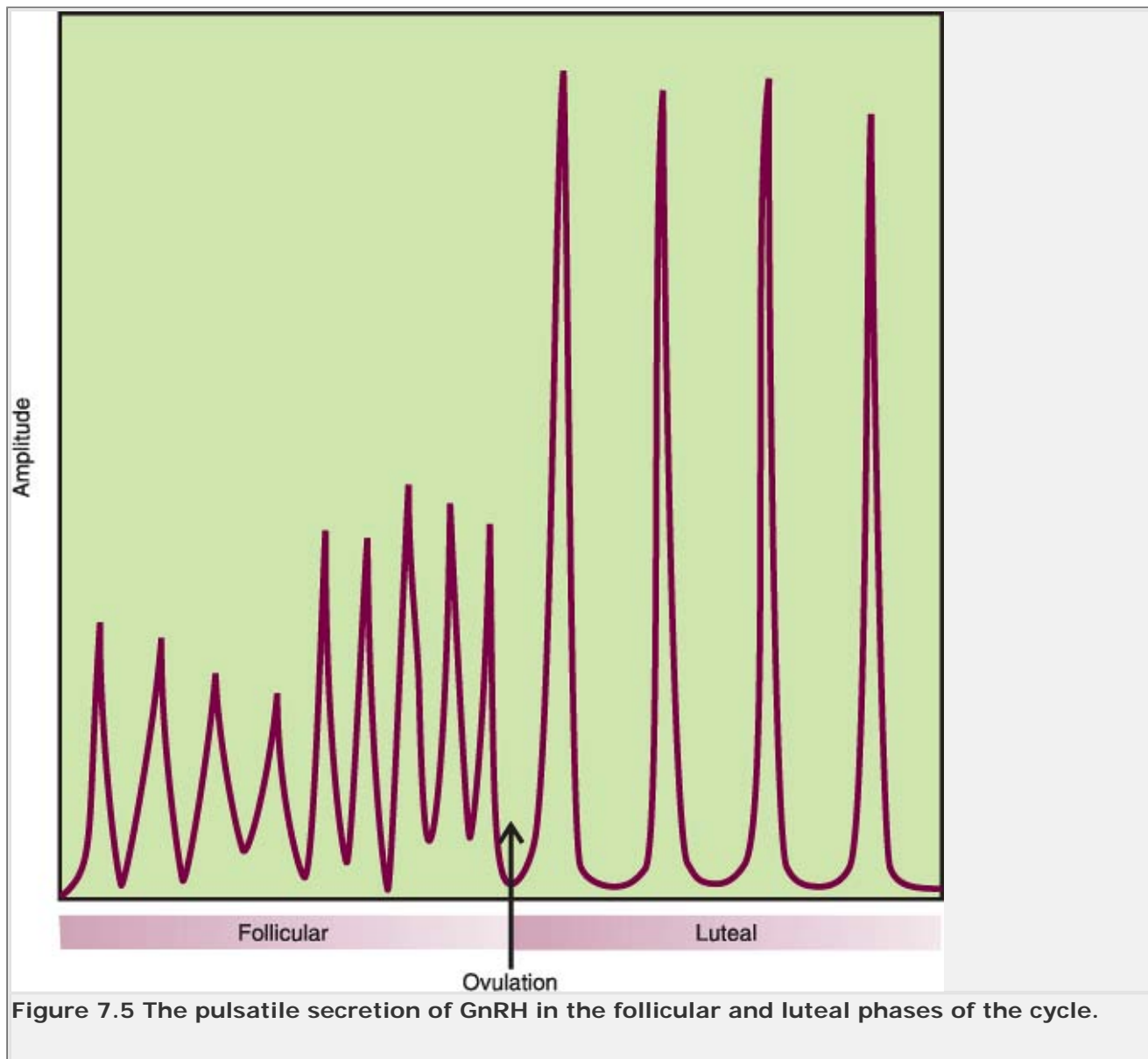


Figure 7.5 The pulsatile secretion of GnRH in the follicular and luteal phases of the cycle.

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Although GnRH is primarily involved in endocrine regulation of gonadotropin secretion from the pituitary, it is now apparent that this molecule has autocrine and paracrine functions throughout the body. The decapeptide is found in both neural and nonneural tissues; receptors are present in many extrapituitary structures, including the ovary and placenta. The role of GnRH in the extrapituitary sites remains to be fully elucidated.

Gonadotropin-releasing Hormone Agonists

Mechanism of Action

Used clinically, GnRH agonists are modifications of the native molecule to either increase receptor affinity or decrease degradation (19). Their use, therefore, leads to a persistent activation of GnRH receptors, as if continuous GnRH exposure existed. As would be predicted by the constant GnRH infusion experiments, this leads to suppression of gonadotropin secretion. An initial release of gonadotropins is followed by a profound suppression of secretion. The

initial release of gonadotropins represents the secretion of pituitary stores in response to receptor binding and activation. With continued activation of the gonadotroph GnRH receptor, however, there is a downregulation effect and a decrease in the concentration of GnRH receptors. As a result, gonadotropin secretion decreases and sex steroid production falls to castrate levels (20).

Additional modification of the GnRH molecule results in an analogue that has no intrinsic activity but competes with GnRH for the same receptor site (21). These GnRH antagonists produce a competitive blockade of GnRH receptors, preventing stimulation by endogenous GnRH and causing an immediate fall in gonadotropin and sex steroid secretion (22). The clinical effect is generally observed within 24 to 72 hours. Moreover, antagonists may not function solely as competitive inhibitors; recent evidence suggests they may also produce downregulation of GnRH receptors (23), further contributing to the loss of gonadotropin activity.

Structure—Agonists and Antagonists

As a peptide hormone, GnRH is degraded by enzymatic cleavage of bonds between its amino acids. Pharmacologic alterations of the structure of GnRH have led to the creation of agonists and antagonists (Fig. 7.4). The primary sites of enzymatic cleavage are between amino acids 5 and 6, 6 and 7, and 9 and 10. Substitution of the position-6 amino acid glycine with large bulky amino acid analogues makes degradation more difficult and creates a form of GnRH with a relatively long half-life. Substitution at the carboxyl terminus produces a form of GnRH with increased receptor affinity. The resulting high affinity and slow degradation produces a molecule that mimics continuous exposure to native GnRH (19). Thus, as with constant GnRH exposure, downregulation occurs. GnRH agonists are now widely used to treat disorders that are dependent on ovarian hormones (20). They are used to control ovulation induction cycles and to treat precocious puberty, ovarian hyperandrogenism, leiomyomas, endometriosis, and hormonally dependent cancers. The development of GnRH antagonists proved more difficult because a molecule was needed that maintained the binding and degradation resistance of agonists but failed to activate the receptor. Early attempts involved modification of amino acids 1 and 2, as well as those previously utilized for agonists. Commercial antagonists currently have structural modifications at amino acids 1, 2, 3, 6, 8, and 10. The treatment spectrum is expected to be similar to that of GnRH agonists, but with more rapid onset of action.

Endogenous Opioids and Effects on GnRH

The endogenous opioids are three related families of naturally occurring substances produced in the CNS that represent the natural ligands for the opioid receptors (24,25,26). **There are three major classes of endogenous opioids**, each derived from precursor molecules:

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- **Endorphins** are named for their endogenous morphinelike activity. These substances are produced in the hypothalamus from the precursor proopiomelanocortin (POMC) and have diverse activities, including regulation of temperature, appetite, mood, and behavior (27).

- **Enkephalins** are the most widely distributed opioid peptides in the brain, and they function primarily in regulation of the autonomic nervous system. Proenkephalin A is the precursor for the two enkephalins of primary importance: methionine-enkephalin and leucine-enkephalin.

Dynorphins are endogenous opioids produced from the precursor proenkephalin B that serve a function similar to that of the endorphins, producing behavioral effects and exhibiting a high analgesic potency.

The endogenous opioids play a significant role in the regulation of hypothalamic–pituitary function. Endorphins appear to inhibit GnRH release within the hypothalamus, resulting in inhibition of gonadotropin secretion (28). Ovarian sex steroids can increase the secretion of central endorphins, further depressing gonadotropin levels (29).

Endorphin levels vary significantly throughout the menstrual cycle, with peak levels in the luteal phase and a nadir during menses (30). This inherent variability, although helping to regulate gonadotropin levels, may contribute to cycle-specific symptoms experienced by ovulatory women. For example, the dysphoria experienced by some women in the premenstrual phase of the cycle may be related to a withdrawal of endogenous opiates (31).

Pituitary Hormone Secretion

Anterior Pituitary

The anterior pituitary is responsible for the secretion of the major hormone-releasing factors—FSH, LH, TSH, and ACTH—as well as GH and prolactin. Each hormone is released by a specific pituitary cell type.

Gonadotropins

The gonadotropins FSH and LH are produced by the anterior pituitary gonadotroph cells and are responsible for ovarian follicular stimulation. Structurally, there is great similarity between FSH and LH (Fig. 7.6). They are both glycoproteins that share identical α subunits and differ only in the structure of their β subunits, which confer receptor specificity (32,33). The synthesis of the β subunits is the rate-regulating step in gonadotropin biosynthesis (34). Thyroid-stimulating hormone and placental human chorionic gonadotropin (hCG) also share identical α subunits with the gonadotropins. There are several forms of each gonadotropin, which differ in carbohydrate content as a result of posttranslational modification. The degree of modification varies with steroid levels and is an important regulator of gonadotropin bioactivity.

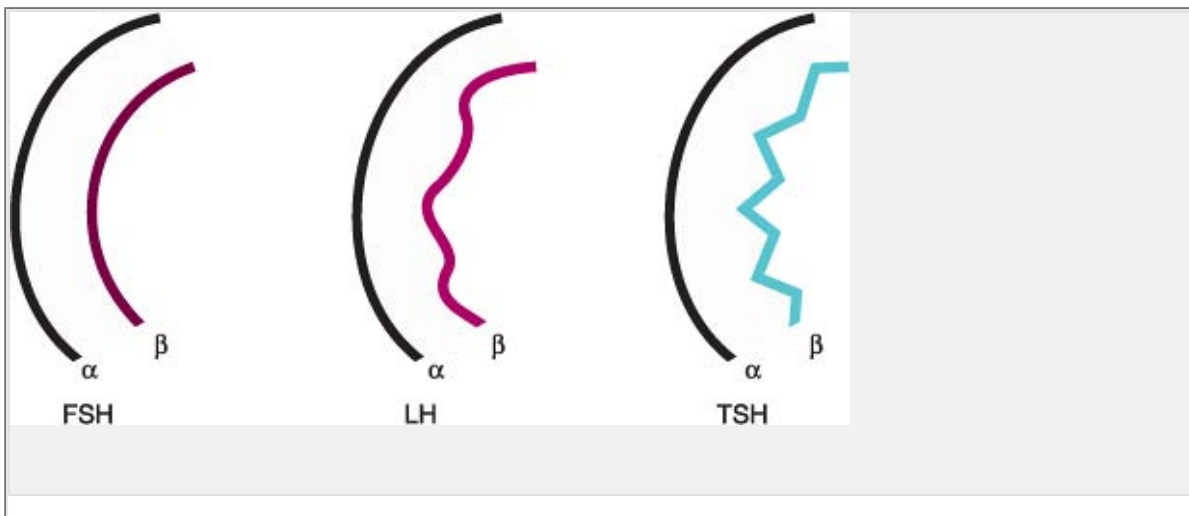


Figure 7.6 The structural similarity between FSH, LH, and TSH. The α subunits are identical and the β subunits differ.

Prolactin

Prolactin, a 198–amino acid polypeptide secreted by the anterior pituitary lactotroph, is the primary trophic factor responsible for the synthesis of milk by the breast (35). Several forms of this hormone, which are named according to their size and bioactivity, are normally secreted (36). Prolactin gene transcription is principally stimulated by estrogen; other hormones promoting transcription are TRH (thyroid-releasing hormone) and a variety of growth factors.

Prolactin secretion is under tonic inhibitory control by the hypothalamic secretion of dopamine (37). Therefore, disease states characterized by decreased dopamine secretion or any condition that interrupts transport of dopamine down the infundibular stalk to the pituitary gland will result in increased synthesis of prolactin. In this respect, prolactin is unique in comparison with all other pituitary hormones: It is predominantly under tonic inhibition, and release of control produces an increase in secretion. **Clinically, increased prolactin levels are associated with amenorrhea and galactorrhea, and hyperprolactinemia should be suspected in any individual with symptoms of either of these conditions.**

Although prolactin appears to be primarily under inhibitory control, many stimuli can elicit its release, including breast manipulation, drugs, stress, exercise, and certain foods. Hormones that may stimulate prolactin release include TRH, vasopressin, γ -aminobutyric acid (GABA), dopamine, β -endorphin, vasoactive intestinal peptide (VIP), epidermal growth factor, angiotensin II, and possibly GnRH (38,39,40). The relative contributions of these substances under normal conditions remain to be determined.

Thyroid-stimulating Hormone, Adrenocorticotrophic Hormone, and Growth Hormone

The other hormones produced by the anterior pituitary are TSH, ACTH, and GH. Thyroid-stimulating hormone is secreted by the pituitary thyrotrophs in response to TRH. As with GnRH, TRH is synthesized primarily in the arcuate nucleus of the hypothalamus and is then secreted into the portal circulation for transport to the pituitary. In addition to stimulating TSH release, TRH is also a major stimulus for the release of prolactin. Thyroid-stimulating hormone stimulates release of T_3 and T_4 from the thyroid gland, which in turn has a negative feedback effect on pituitary TSH secretion. Abnormalities of thyroid secretion (both hyper- and hypothyroidism) are frequently associated with ovulatory dysfunction as a result of diverse actions on the hypothalamic–pituitary–ovarian axis (41).

Adrenocorticotrophic hormone is secreted by the anterior pituitary in response to another hypothalamic-releasing factor, CRH, and stimulates the release of adrenal glucocorticoids. Unlike the other anterior pituitary products, ACTH secretion has a diurnal variation with an early morning peak and a late evening nadir. As with the other pituitary hormones, ACTH secretion is negatively regulated by feedback from its primary end product, which in this case is cortisol.

The anterior pituitary hormone that is secreted in the greatest absolute amount is GH. It is secreted in response to the hypothalamic-releasing factor, GHRH, as well as by thyroid hormone and glucocorticoids. This hormone is also secreted in a pulsatile fashion but with

peak release occurring during sleep. In addition to its vital role in the stimulation of linear growth, GH plays a diverse role in physiologic hemostasis. The hormone has been shown

to play a role in bone mitogenesis, CNS function (improved memory, cognition, and mood), body composition, breast development, and cardiovascular function. It also affects insulin regulation and acts anabolically. Growth hormone appears to have a role in the regulation of ovarian function, although the degree to which it serves this role in normal physiology is unclear (42).

Posterior Pituitary

Structure and Function

The posterior pituitary (neurohypophysis) is composed exclusively of neural tissue and is a direct extension of the hypothalamus. It lies directly adjacent to the adenohypophysis but is embryologically distinct, derived from an invagination of neuroectodermal tissue in the third ventricle. Axons in the posterior pituitary originate from neurons with cell bodies in two distinct regions of the hypothalamus, the supraoptic and paraventricular nuclei, named for their anatomic relationship to the optic chiasm and the third ventricle. Together these two nuclei compose the hypothalamic magnocellular system. These neurons can secrete their synthetic products directly from axonal boutons into the general circulation to act as hormones. This is the mechanism of secretion of the hormones of the posterior pituitary, oxytocin and arginine vasopressin (AVP). Although this is the primary mode of release of these hormones, numerous other secondary pathways have been identified, including secretion into the portal circulation, intrahypothalamic secretion, and secretion into other regions of the CNS (43).

In addition to the established functions of oxytocin and vasopressin, several other diverse roles have been suggested in animal models. These functions include modulation of sexual activity and appetite, learning and memory consolidation, temperature regulation, and regulation of maternal behaviors (44). It remains to be seen which, if any, of these functions also exist in humans.

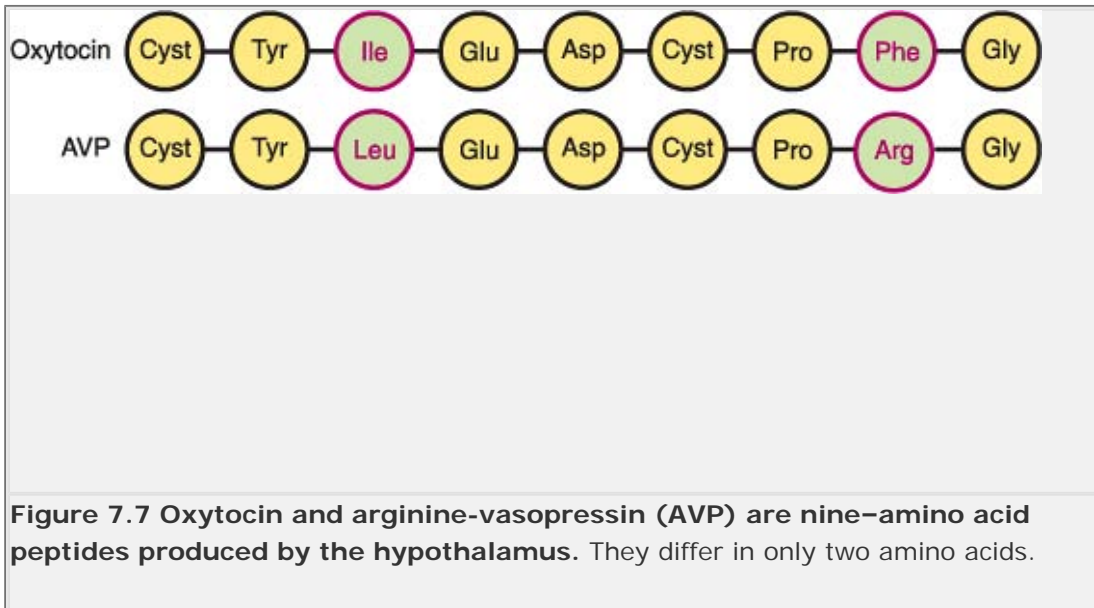
Oxytocin

Oxytocin is a nine–amino acid peptide primarily produced by the paraventricular nucleus of the hypothalamus (Fig. 7.7). The primary function of this hormone in humans is the stimulation of two specific types of muscular contractions (Fig. 7.8). The first type, uterine muscular contraction, occurs during parturition. The second type of muscular contraction regulated by oxytocin is breast lactiferous duct myoepithelial contractions, which occur during the milk letdown reflex. Oxytocin release may be stimulated by suckling, triggered by a signal from nipple stimulation transmitted via thoracic nerves to the spinal cord and then to the hypothalamus, where oxytocin is released in an episodic fashion (45). Oxytocin release also may be triggered by olfactory, auditory, and visual clues, and it may play a role in the conditioned reflex in nursing animals. Stimulation of the cervix and vagina can cause significant release of oxytocin, which may trigger reflex ovulation (the Ferguson reflex) in some species.

Arginine-vasopressin

Also known as antidiuretic hormone, or ADH, AVP is the second major secretory product of the posterior pituitary (Fig. 7.7). It is synthesized primarily by neurons with cell bodies in

the supraoptic nuclei (Fig. 7.8). Its major function is the regulation of circulating blood volume, pressure, and osmolality (45). Specific receptors throughout the body can trigger the release of AVP. Osmoreceptors located in the hypothalamus sense changes in blood osmolality from a mean of 285 mOSM/kg. Baroreceptors sense changes in blood pressure caused by alterations in blood volume and are peripherally located in the walls of the left atrium, carotid sinus, and aortic arch (46). These receptors can respond to changes in blood volume of more than 10%. In response to decreases in blood pressure or volume, AVP is released and causes arteriolar vasoconstriction and renal free-water conservation. This in turn leads to a decrease in blood osmolality and an increase in blood pressure. Activation of the renal renin–angiotensin system can also activate AVP release.



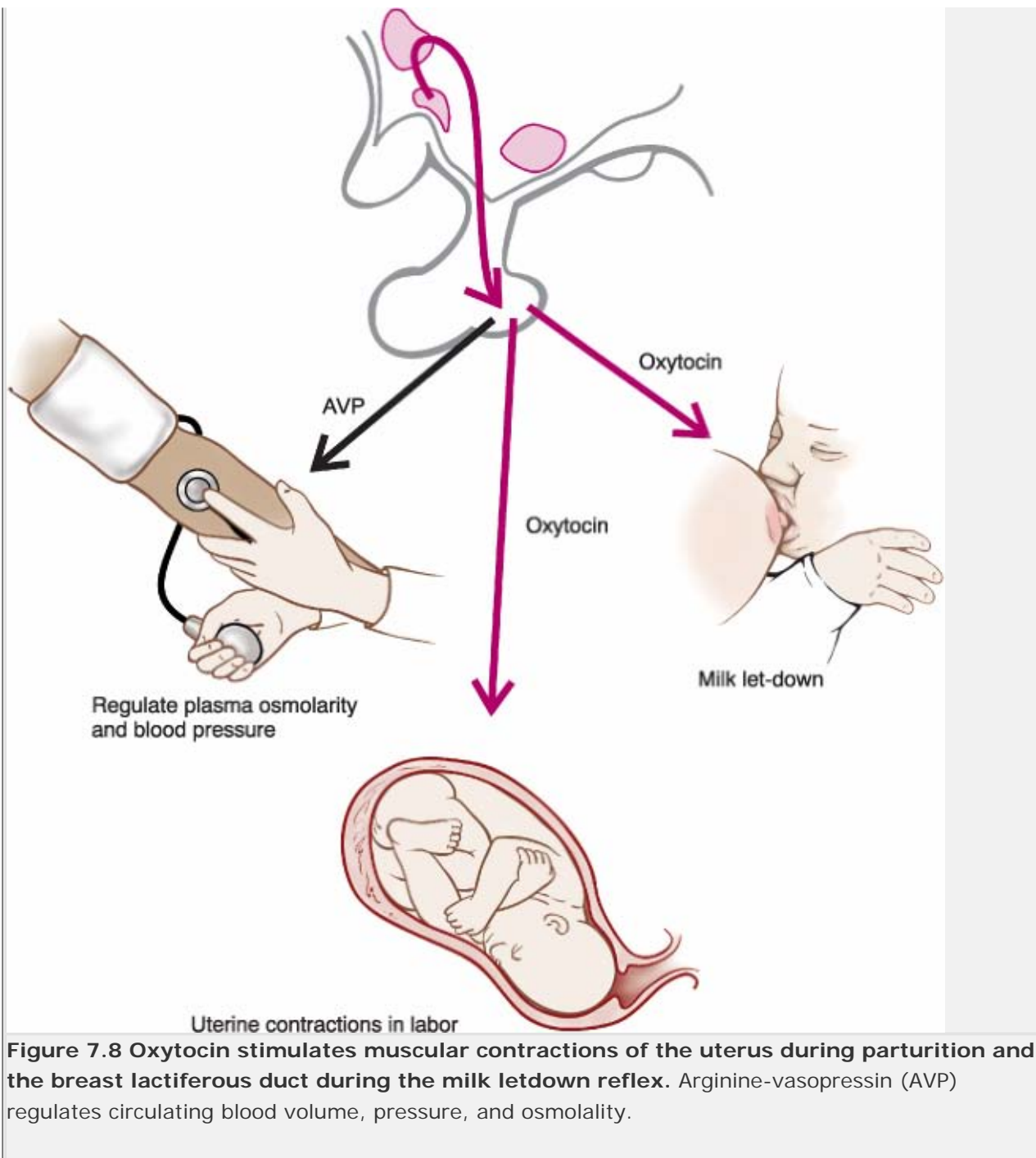


Figure 7.8 Oxytocin stimulates muscular contractions of the uterus during parturition and the breast lactiferous duct during the milk letdown reflex. Arginine-vasopressin (AVP) regulates circulating blood volume, pressure, and osmolality.

Menstrual Cycle Physiology

In the normal menstrual cycle, orderly cyclic hormone production and parallel proliferation of the uterine lining prepare for implantation of the embryo. Disorders of the

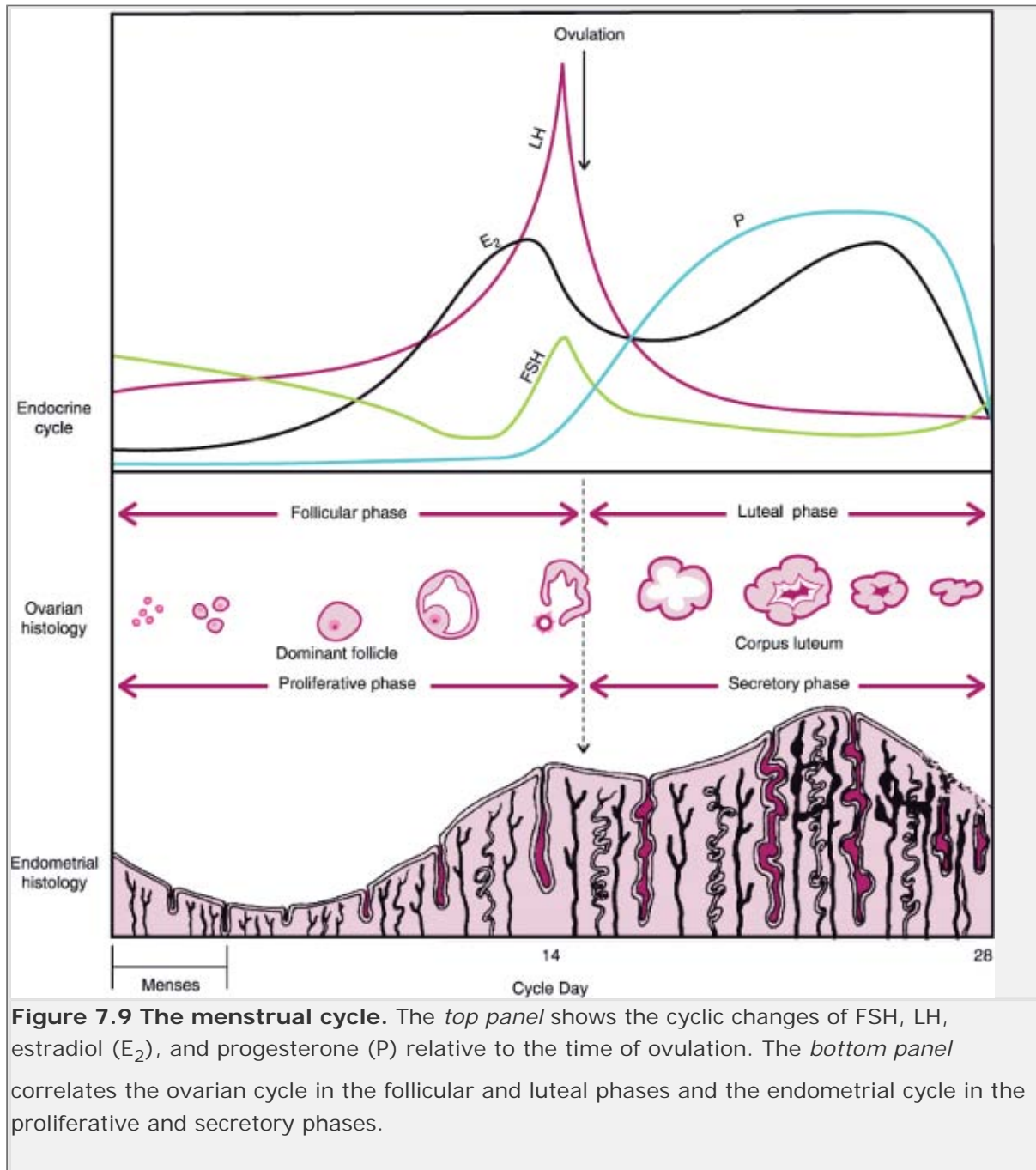
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menstrual cycle and, likewise, disorders of menstrual physiology may lead to various pathologic states, including infertility, recurrent miscarriage, and malignancy.

Normal Menstrual Cycle

The normal human menstrual cycle can be divided into two segments: the ovarian cycle and the uterine cycle, based on the organ under examination. The ovarian cycle may be further divided into follicular and luteal phases, whereas the uterine cycle

is divided into corresponding proliferative and secretory phases (Fig. 7.9). The phases of the ovarian cycle are characterized as follows:



- **Follicular phase**— hormonal feedback promotes the orderly development of a single dominant follicle, which should be mature at midcycle and prepared for ovulation. The average length of the human follicular phase ranges from 10 to 14 days, and variability in this length is responsible for most variations in total cycle length.

- **Luteal phase**— the time from ovulation to the onset of menses has an average length of 14 days.

A normal menstrual cycle lasts from 21 to 35 days, with 2 to 6 days of flow and an average blood loss of 20 to 60 mL. However, studies of large numbers of women with normal menstrual cycles have shown that only approximately two thirds of adult women have cycles lasting 21 to 35 days (47). The extremes of reproductive life (after menarche and perimenopause) are characterized by a higher percentage of anovulatory or irregularly timed cycles (48,49).

Hormonal Variations

The relative pattern of ovarian, uterine, and hormonal variation along the normal menstrual cycle is shown in Fig. 7.9.

- **At the beginning of each monthly menstrual cycle, levels of gonadal steroids are low and have been decreasing since the end of the luteal phase of the previous cycle.**
- **With the demise of the corpus luteum, FSH levels begin to rise, and a cohort of growing follicles is recruited.** These follicles each secrete increasing levels of estrogen as they grow in the follicular phase. The increase in estrogen, in turn, is the stimulus for uterine endometrial proliferation.
- **Rising estrogen levels provide negative feedback on pituitary FSH secretion, which begins to wane by the midpoint of the follicular phase.** In addition, the growing follicles produce inhibin-B, which also suppresses FSH secretion by the pituitary. Conversely, LH initially decreases in response to rising estradiol levels, but late in the follicular phase the LH level is increased dramatically (biphasic response).
- **At the end of the follicular phase (just before ovulation), FSH-induced LH receptors are present on granulosa cells and, with LH stimulation, modulate the secretion of progesterone.**
- **After a sufficient degree of estrogenic stimulation, the pituitary LH surge is triggered, which is the proximate cause of ovulation that occurs 24 to 36 hours later.** Ovulation heralds the transition to the luteal–secretory phase.
- **The estrogen level decreases through the early luteal phase from just before ovulation until the midluteal phase, when it begins to rise again as a result of corpus luteum secretion.** Similarly, inhibin-A is secreted by the corpus luteum.
- **Progesterone levels rise precipitously after ovulation and can be used as a presumptive sign that ovulation has occurred.**
- **Progesterone, estrogen, and inhibin-A act centrally to suppress gonadotropin secretion and new follicular growth.** These hormones remain elevated through the lifespan of the corpus luteum and then wane with its demise, thereby setting the stage for the next cycle.

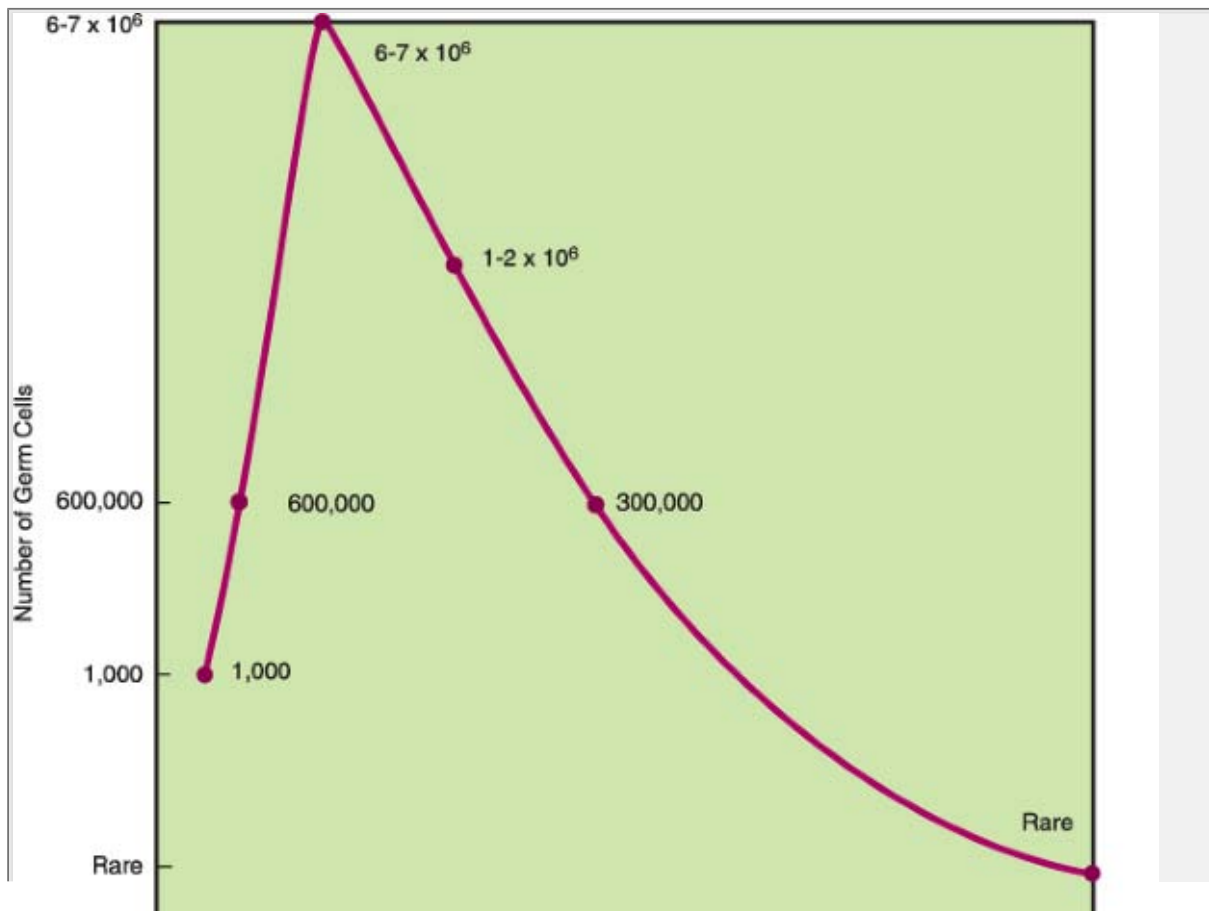
Uterus

Cyclic Changes of the Endometrium

In 1950, Noyes, Hertig, and Rock described the cyclic histologic changes in the adult human endometrium (50) (Fig. 7.10). These changes proceed in an orderly fashion in response to cyclic hormonal production by the ovaries (Fig. 7.9). Histologic cycling of the endometrium can best be viewed in two parts: the endometrial glands and the surrounding stroma.

The superficial two thirds of the endometrium is the zone that proliferates and is ultimately shed with each cycle if pregnancy does not occur. This cycling portion of the endometrium is known as the *decidua functionalis* and is composed of a deeply situated intermediate zone (stratum spongiosum) and a superficial compact zone (stratum compactum). The *decidua basalis* is the deepest region of the endometrium. It does not undergo significant monthly proliferation but, instead, is the source of endometrial regeneration after each menses (51).

The existence of endometrial stem cells has long been assumed but has proven difficult to document. Recently, researchers found a small population of human epithelial and stromal cells that possess clonogenicity, suggesting that they represent the putative endometrial stem cells (52). Further evidence of the existence of such cells, as well as their source, was provided by another study that showed endometrial glandular epithelial cells obtained from endometrial biopsies of women undergoing bone marrow transplants express the HLA type of the donor bone marrow (53). This finding suggests that not only do endometrial stem cells exist, but also that they reside in bone marrow and migrate to the basalis of the endometrium. Furthermore, the timing of the appearance of these cells following the transplant was as long as several years. This fact may prove to be of clinical importance in patients with Asherman's Syndrome who experienced a loss of functional endometrium; repair of the uterine anatomy may eventually result in a functioning endometrial cavity.



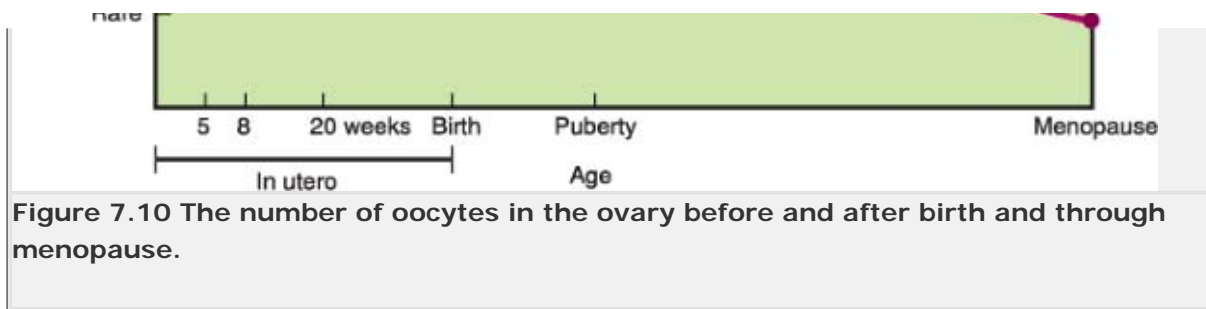


Figure 7.10 The number of oocytes in the ovary before and after birth and through menopause.

Proliferative Phase

By convention, the first day of vaginal bleeding is called day 1 of the menstrual cycle.

After menses, the decidua basalis is composed of primordial glands and dense scant stroma in its location adjacent to the myometrium. The proliferative phase is characterized by progressive mitotic growth of the decidua functionalis in preparation for implantation of the embryo in response to rising circulating levels of estrogen (54). At the beginning of the proliferative phase, the endometrium is relatively thin (1–2 mm). The predominant change seen during this time is evolution of the initially straight, narrow, and short endometrial glands into longer, tortuous structures (55). Histologically, these proliferating glands have multiple mitotic cells, and their organization changes from a low columnar pattern in the early proliferative period to a pseudostratified pattern before ovulation. Throughout this time, the stroma is a dense compact layer, and vascular structures are infrequently seen.

Secretory Phase

In the typical 28-day cycle, ovulation occurs on cycle day 14. Within 48 to 72 hours following ovulation, the onset of progesterone secretion produces a shift in histologic appearance of the endometrium to the secretory phase, so named for the clear presence of eosinophilic protein-rich secretory products in the glandular lumen. In contrast to the proliferative phase, the secretory phase of the menstrual cycle is characterized by the cellular effects of progesterone in addition to estrogen. In general, progesterone's effects are antagonistic to those of estrogen, and there is a progressive decrease in the endometrial cell's estrogen receptor concentration. As a result, during the latter half of the cycle, estrogen-induced DNA synthesis and cellular mitosis are antagonized (54).

During the secretory phase, the endometrial glands form characteristic periodic acid–Schiff positive–staining, glycogen-containing vacuoles. These vacuoles initially appear subnuclearly and then progress toward the glandular lumen (50) (Fig. 7.10). The nuclei can be seen in the midportion of the cells and ultimately undergo apocrine secretion into the glandular lumen, often by cycle day 19–20. At postovulatory day 6–7, secretory activity of the glands is generally maximal, and the endometrium is optimally prepared for implantation of the blastocyst.

The stroma of the secretory phase remains unchanged histologically until approximately the seventh postovulatory day, when there is a progressive increase in edema. Coincident with maximal stromal edema in the late secretory phase, the spiral arteries become clearly visible and then progressively lengthen and coil during the remainder of the secretory phase. By around day 24, an eosinophilic-staining pattern, known as *cuffing*, is visible in the perivascular stroma. Eosinophilia then progresses to form islands in the stroma followed by areas of confluence. This staining pattern of the edematous stroma is termed *pseudodecidual* because of its similarity to the pattern that occurs in

pregnancy. Approximately 2 days before menses, there is a dramatic increase in the number of polymorphonuclear lymphocytes that migrate from the vascular system. This leukocytic infiltration heralds the collapse of the endometrial stroma and the onset of the menstrual flow.

Menses

In the absence of implantation, glandular secretion ceases, and an irregular breakdown of the *decidua functionalis* occurs. The resultant shedding of this layer of the

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endometrium is termed *menses*. The destruction of the corpus luteum and its production of estrogen and progesterone is the presumed cause of the shedding.

With withdrawal of sex steroids, there is a profound spiral artery vascular spasm that ultimately leads to endometrial ischemia. Simultaneously, there is a breakdown of lysosomes and a release of proteolytic enzymes, which further promote local tissue destruction. This layer of endometrium is then shed, leaving the decidua basalis as the source of subsequent endometrial growth. Prostaglandins are produced throughout the menstrual cycle and are at their highest concentration during menses (53). Prostaglandin F_{2α} (PGF_{2α}) is a potent vasoconstrictor, causing further arteriolar vasospasm and endometrial ischemia. PGF_{2α} also produces myometrial contractions that decrease local uterine wall blood flow and may serve to physically expel sloughing endometrial tissue from the uterus.

Dating the Endometrium

The changes seen in secretory endometrium relative to the LH surge have long been thought to allow the assessment of the "normalcy" of endometrial development. Since 1950, it was felt that by knowing when a patient ovulated, it was possible to obtain a sample of endometrium by endometrial biopsy and determine whether the state of the endometrium corresponds to the appropriate time of the cycle. Traditional thinking held that any discrepancy of more than 2 days between chronologic and histologic date indicated a pathologic condition termed luteal phase defect; this abnormality has been linked to both infertility (via implantation failure) and early pregnancy loss (56).

Recent evidence, however, suggests a lack of utility for the endometrial biopsy as a diagnostic test for either infertility or early pregnancy loss (56). In a randomized, observational study of regularly cycling, fertile women, it was found that endometrial dating is far less accurate and precise than originally claimed, and does not provide a valid method for the diagnosis of luteal phase defect (57). Furthermore, a large prospective, multicenter trial sponsored by the National Institutes of Health showed that histologic dating of the endometrium does not discriminate between fertile and infertile women (58). Thus, after half a century of using this test in the evaluation of the subfertile couple, it has become clear that today the endometrial biopsy has no role in the routine evaluation of infertility or early pregnancy loss.

Ovarian Follicular Development

The number of oocytes peaks in the fetus at 6 to 7 million by 20 weeks of gestation (59) (Fig. 7.10). Simultaneously (and peaking at the fifth month of gestation), atresia of the oogonia occurs, rapidly followed by follicular atresia. At birth, only 1 to 2 million oocytes remain in the ovaries, and **at puberty, only 300,000 of the original 6 to 7 million oocytes are available for ovulation** (59,60). **Of these, only 400 to 500 will ultimately be released during ovulation.** By the time of menopause, the ovary will be composed primarily of dense stromal tissue with only rare interspersed oocytes remaining.

A central dogma of reproductive biology is that in mammalian females there is no capacity for oocyte production postnatally. Because oocytes enter the diplotene resting stage of meiosis in the fetus and persist in this stage until ovulation, much of the deoxyribonucleic acid (DNA), proteins, and messenger ribonucleic acid (mRNA) necessary for development of the preimplantation embryo will have been synthesized by this stage. At the diplotene stage, a single layer of 8 to 10 granulosa cells surround the oogonia to form the primordial follicle. The oogonia that fail to become properly surrounded by granulosa cells undergo atresia (61). The remainder proceed with follicular development. Thus, most oocytes are lost during fetal development, and the remaining follicles are steadily "used up" throughout the intervening years until menopause.

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Recent evidence has begun to challenge this theory. Studies in the mouse have shown that production of oocytes and corresponding folliculogenesis can occur well into adult life (62). The reservoir of germline stem cells responsible for this oocyte development appears to reside in the bone marrow (63). It is not clear whether such stem cells exist in adult humans, and if they do, what clinical function they might provide.

Meiotic Arrest of Oocyte and Resumption

Meiosis (the germ cell process of reduction division) is commonly divided into four phases: **prophase, metaphase, anaphase, and telophase**. The **prophase of meiosis I** is further divided into five stages: ***leptotene, zygotene, pachytene, diplotene, and diakinesis***.

Oogonia differ from spermatogonia in that only one final daughter cell (oocyte) forms from each precursor cell, with the excess genetic material discarded in three polar bodies. When the developing oogonia begin to enter meiotic prophase I, they are known as primary oocytes (64). This process begins at roughly 8 weeks of gestation. Only those oogonia that enter meiosis will survive the wave of atresia that sweeps the fetal ovary before birth. The oocytes arrested in prophase (in the late diplotene or "dictyate" stage) will remain so until the time of ovulation, when the process of meiosis resumes. The mechanism for this mitotic stasis is believed to be an oocyte maturation inhibitor (OMI) produced by granulosa cells (65). This inhibitor gains access to the oocyte via gap junctions connecting the oocyte and its surrounding cumulus of granulosa. With the midcycle LH surge, the gap junctions are disrupted, granulosa cells are no longer connected to the oocyte, and meiosis I is allowed to resume.

Follicular Development

Follicular development is a dynamic process that continues from menarche until menopause. The process is designed to allow the monthly recruitment of a cohort of follicles and, ultimately, to release a single mature dominant follicle during ovulation each month.

Primordial Follicles

The initial recruitment and growth of the primordial follicles is gonadotropin independent and affects a cohort over several months (66). However, the stimuli responsible for the recruitment of a specific cohort of follicles in each cycle are unknown. At the primordial follicle stage, shortly after initial recruitment, FSH assumes control of follicular differentiation and growth and allows a cohort of follicles to continue differentiation.

This process signals the shift from gonadotropin-independent to gonadotropin-dependent growth. The first changes seen are growth of the oocyte and expansion of the single layer of follicular granulosa cells into a multilayer of cuboidal cells. The decline in luteal phase estrogen, progesterone, and inhibin-A production by the now-fading corpus luteum from the previous cycle allows the increase in FSH that stimulates this follicular growth (67).

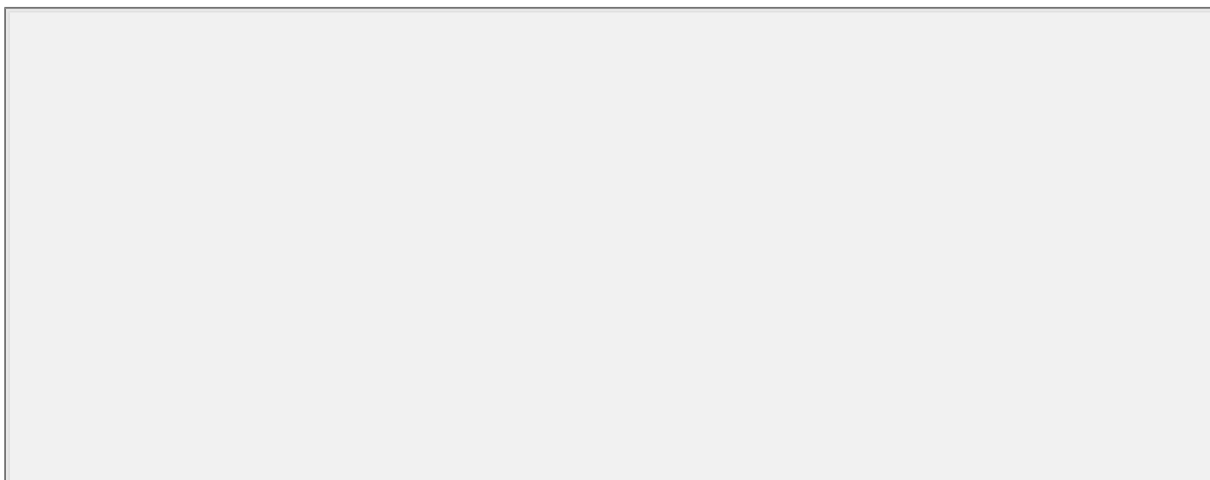
Preantral Follicle

During the several days following the breakdown of the corpus luteum, growth of the cohort of follicles continues, driven by the stimulus of FSH. The enlarging oocyte then secretes a glycoprotein-rich substance, the zona pellucida, which separates it from the surrounding granulosa cells (except for the aforementioned gap junction). With transformation from a primordial to a preantral follicle, there is continued mitotic proliferation of the encompassing granulosa cells. Simultaneously, theca cells in the stroma bordering the granulosa cells proliferate. Both cell types function synergistically to produce estrogens that are secreted into the systemic circulation. At this stage of development, each of the seemingly identical cohort members must either be selected for dominance or undergo atresia. It is likely that the follicle destined to ovulate has been selected before this point, although the mechanism for selection remains obscure.

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Two-cell Two-gonadotropin Theory

The fundamental tenet of follicular development is the two-cell, two-gonadotropin theory (66,68,69) (Fig. 7.11). This theory states that there is a subdivision and compartmentalization of steroid hormone synthesis activity in the developing follicle. In general, most aromatase activity (for estrogen production) is in the granulosa cells (70). Aromatase activity is enhanced by FSH stimulation of specific receptors on these cells (71,72). However, granulosa cells lack several enzymes that occur earlier in the steroidogenic pathway and require androgens as a substrate for aromatization. Androgens, in turn, are synthesized primarily in response to stimulation by LH, and the theca cells possess most of the LH receptors at this stage (71,72). Therefore, a synergistic relationship must exist: LH stimulates the theca cells to produce androgens (primarily androstenedione), which in turn are transferred to the granulosa cells for FSH-stimulated aromatization into estrogens. These locally produced estrogens create a microenvironment within the follicle that is favorable for continued growth and nutrition (73). Both FSH and local estrogens serve to further stimulate estrogen production, FSH receptor synthesis and expression, and granulosa cell proliferation and differentiation.



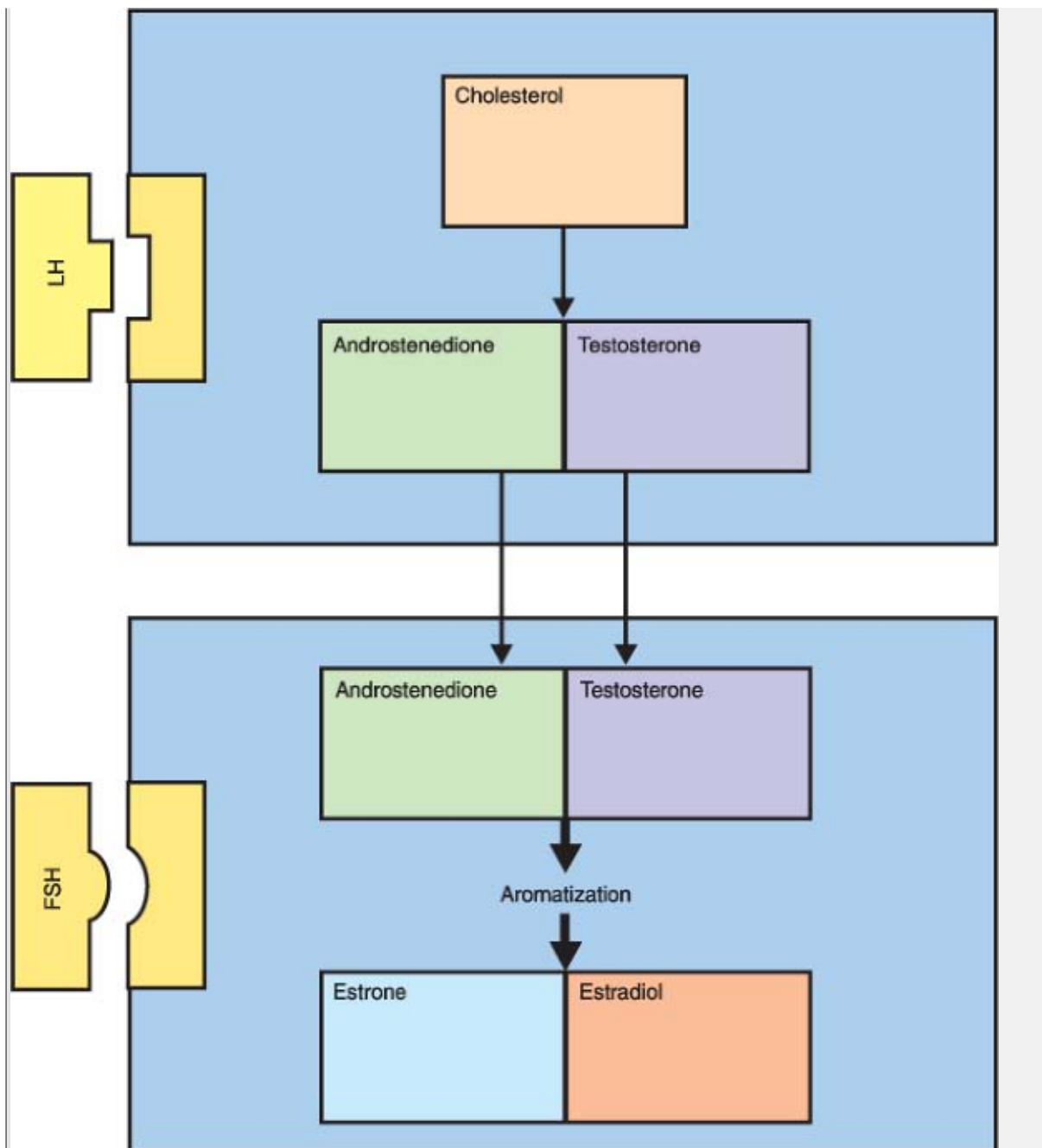


Figure 7.11 The two-cell, two-gonadotropin theory of follicular development in which there is compartmentalization of steroid hormone synthesis in the developing follicle.

Androgens have two different regulatory roles in follicular development. At low concentrations (i.e., in the early preantral follicle), they serve to stimulate aromatase activity via specific receptors in granulosa cells. At higher levels of androgens, there is intense 5 α -reductase activity that converts the androgens to forms that cannot be aromatized (68,74). This androgenic microenvironment inhibits the expression of FSH receptors on the granulosa cells, thereby inhibiting aromatase activity and setting the follicle on the path to atresia (75). Meanwhile, as the peripheral estrogen level rises, it negatively feeds back on the pituitary and hypothalamus to decrease circulating FSH levels (76). Increased ovarian production of inhibin-B further decreases FSH production at this point.

The falling FSH level that occurs with the progression of the follicular phase represents a threat to continued follicular growth. The resulting adverse environment can be

withstood only by follicles with a selective advantage for binding the diminishing FSH molecules; that is, those with the greatest number of FSH receptors. The dominant follicle, therefore, can be perceived as the one with a richly estrogenic microenvironment and the most FSH receptors (77). As it grows and develops, the follicle continues to produce estrogen, which results in further lowering of the circulating FSH and creating a more adverse environment for competing follicles. This process continues until all members of the initial cohort, with the exception of the single dominant follicle, have suffered atresia. The stage is then set for ovulation.

Preovulatory Follicle

Preovulatory follicles are characterized by a fluid-filled antrum that is composed of plasma with granulosa-cell secretions. The granulosa cells at this point have further differentiated into a heterogenous population. The oocyte remains connected to the follicle by a stalk of specialized granulosa known as the *cumulus oophorus*.

Rising estrogen levels have a negative feedback effect on FSH secretion. Conversely, LH undergoes biphasic regulation by circulating estrogens. At lower concentrations, estrogens inhibit LH secretion. At higher levels, however, estrogen enhances LH release. This stimulation requires a sustained high level of estrogen (200 pg/mL) for more than 48 hours (78). Once the rising estrogen level produces positive feedback, a substantial surge in LH secretion occurs. Concomitant to these events, the local estrogen-FSH interactions in the dominant follicle induce LH receptors on the granulosa cells. Thus, exposure to high levels of LH results in a specific response by the dominant follicle—the result is luteinization of the granulosa cells, production of progesterone, and initiation of ovulation. In general, ovulation will occur in the single mature, or Graafian, follicle 10 to 12 hours after the LH peak or 34 to 36 hours after the initial rise in midcycle LH (79,80,81).

As suggested previously, the sex steroids are not the only gonadotropin regulators of follicular development. Two related granulosa cell-derived peptides have been identified that play opposing roles in pituitary feedback (82). **The first of these peptides, inhibin, is secreted in two forms: inhibin-A and inhibin-B.** Inhibin-B is secreted primarily in the follicular phase and is stimulated by FSH (83), whereas inhibin-A is mainly active in the luteal phase. **Both forms of inhibin act to inhibit FSH synthesis and release** (84,85). The second peptide, activin, stimulates FSH release from the pituitary gland and potentiates its action in the ovary (86,87). It is likely that there are numerous other intraovarian regulators similar to inhibin and activin, each of which may play a key role in promoting the normal ovulatory process (88). Some of these include follistatin, insulinlike growth factor (ILGF)-1, epidermal growth factor (EGF)/transforming growth factor (TGF)- α , TGF- β 1, β -fibroblast growth factor (FGF), interleukin-1, tissue necrosis factor- α , OMI, and renin-angiotensin.

Ovulation

The midcycle LH surge is responsible for a dramatic increase in local concentrations of prostaglandins and proteolytic enzymes in the follicular wall (89). These substances progressively weaken the follicular wall and ultimately allow a perforation to form. Ovulation most likely represents a slow extrusion of the oocyte through this opening in the follicle rather than a rupture of the follicular structure (90). In fact, direct measurements of intrafollicular pressures have been recorded and have failed to demonstrate an explosive event.

Luteal Phase

Structure of Corpus Luteum

After ovulation, the remaining follicular shell is transformed into the primary regulator of the luteal phase: the corpus luteum. Membranous granulosa cells remaining in the follicle begin to take up lipids and the characteristic yellow lutein pigment for which the structure is named. These cells are active secretory structures that produce progesterone, which supports the endometrium of the luteal phase. In addition, estrogen and inhibin A are produced in significant quantities. Unlike the process that occurs in the developing follicle, the basement membrane of the corpus luteum degenerates to allow proliferating blood vessels to invade the granulosa-luteal cells in response to secretion of angiogenic factors such as vascular endothelial growth factor (91). This angiogenic response allows large amounts of luteal hormones to enter the systemic circulation.

Hormonal Function and Regulation

The hormonal changes of the luteal phase are characterized by a series of negative feedback interactions designed to lead to regression of the corpus luteum if pregnancy does not occur. Corpus luteum steroids (estradiol and progesterone) provide negative central feedback and cause a decrease in FSH and LH secretion. Continued secretion of both steroids will decrease the stimuli for subsequent follicular recruitment. Similarly, luteal secretion of inhibin also potentiates FSH withdrawal. In the ovary, local production of progesterone inhibits the further development and recruitment of additional follicles.

Continued corpus luteum function depends on continued LH production. In the absence of this stimulation, the corpus luteum will invariably regress after 12 to 16 days and form the scarlike *corpora albicans* (92). The exact mechanism of luteolysis, however, is unclear and most likely also involves local paracrine factors. In the absence of pregnancy, the corpus luteum regresses, and estrogen and progesterone levels wane. This, in turn, removes central inhibition on gonadotropin secretion and allows FSH and LH levels to again rise and recruit another cohort of follicles.

If pregnancy does occur, placental hCG will mimic LH action and continually stimulate the corpus luteum to secrete progesterone. Thus, successful implantation results in hormonal support to allow continued maintenance of the corpus luteum and the endometrium. Evidence from patients undergoing oocyte donation cycles has demonstrated that continued luteal function is essential to continuation of the pregnancy until approximately 5 weeks of gestation, when sufficient progesterone is produced by the developing placenta (93). This switch in the source of regulatory progesterone production is referred to as the luteal-placental shift.

Summary of Menstrual Cycle Regulation

Following is a summary of the regulation of the menstrual cycle:

- **GnRH is produced in the arcuate nucleus of the hypothalamus and secreted in a pulsatile fashion into the portal circulation, where it travels to the anterior pituitary.**

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- **Ovarian follicular development moves from a period of gonadotropin independence to a phase of FSH dependence.**

- **As the corpus luteum of the previous cycle fades, luteal production of progesterone and inhibin A decreases, allowing FSH levels to rise.**
- **In response to FSH stimulus, the follicles grow and differentiate and secrete increasing amounts of estrogen and inhibin-B.**
- **Estrogen stimulates growth and differentiation of the functional layer of the endometrium, which prepares for implantation. Estrogens work with FSH in stimulating follicular development.**
- **The two-cell two-gonadotropin theory dictates that with LH stimulation, the ovarian theca cells will produce androgens that are converted by the granulosa cells into estrogens under the stimulus of FSH.**
- **Rising estrogen and inhibin levels negatively feed back on the pituitary gland and hypothalamus and decrease the secretion of FSH.**
- **The one follicle destined to ovulate each cycle is called the dominant follicle. It has relatively more FSH receptors and produces a larger concentration of estrogens than the follicles that will undergo atresia. It is able to continue to grow despite falling FSH levels.**
- **Sustained high estrogen levels cause a surge in pituitary LH secretion that triggers ovulation, progesterone production, and the shift to the secretory, or luteal, phase.**
- **Luteal function is dependent on the presence of LH. However, the corpus luteum secretes estrogen, progesterone, and inhibin-A, which serve to maintain gonadotropin suppression. Without continued LH secretion, the corpus luteum will regress after 12 to 16 days. The resulting loss of progesterone secretion results in menstruation.**
- **If pregnancy occurs, the embryo secretes hCG, which mimics the action of LH by sustaining the corpus luteum. The corpus luteum continues to secrete progesterone and supports the secretory endometrium, allowing the pregnancy to continue to develop.**

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8

Preventive Health Care and Screening

Paula J. Adams Hillard



- **Preventive health services that encompass screening and counseling for a broad range of health behaviors and risks are important components of general obstetric and gynecologic care.**
- **Traditional gynecologic care—including cervical cytology testing, pelvic and breast screening examinations, and the provision of contraceptive services—is considered primary preventive care.**
- **Routine health care assessments for healthy women include a medical history, physical examination, routine and indicated lab studies, assessment and counseling regarding healthy behaviors, and relevant interventions, taking into account the leading causes of morbidity and mortality within different age groups.**
- **Evidence-based guidelines for the provision of periodic health evaluations, screening, and counseling have been developed by the American College of Obstetricians and Gynecologists (ACOG) and other organizations; these guidelines provide the basis for routine preventive health assessment and screening recommendations.**

- **Preventive services for adolescents should be based on knowledge of the behavioral and medical health risks that place their future health at risk, including substance use and abuse, sexual behaviors that increase the risks of unintended pregnancy and sexually transmitted diseases (STDs), and impaired mental health.**
- **Obesity, smoking, and alcohol abuse are preventable problems that have a major impact on long-term health; assessment, counseling, and referral for these health risks is a component of periodic health assessment and primary care.**

Although obstetrician-gynecologists have focused on the management of abnormal gynecologic conditions, they also have a traditional role of providing primary and preventive

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care to women. **Primary care emphasizes health maintenance, preventive services, early detection of disease, and availability and continuity of care (1). The value of preventive services is apparent in such trends as the reduced mortality rate from cervical cancer, in large part resulting from the increased use of cervical cytology testing.** Neonatal screening for phenylketonuria (PKU) and hypothyroidism are examples of effective mechanisms for prevention of mental retardation. Women often regard their gynecologist as their primary care provider; indeed, many women of reproductive age have had no other physician. As primary care physicians, obstetrician-gynecologists provide ongoing care for women through all stages of their lives—from reproductive age to postmenopause. In this role, some gynecologists include as a routine part of their practices screening for certain medical conditions, such as hypertension, diabetes mellitus, and thyroid disease, as well as management of those conditions in the absence of complications.

Some traditional aspects of gynecologic practice, such as family planning and preconception counseling, can be considered preventive health care. Preventive medical services encompass screening and counseling for a broad range of health behaviors and risks, including sexual practices; prevention of STDs; use of tobacco, alcohol, and other drugs; diet; and exercise.

The Institute of Medicine has defined primary care as *"the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community."* Integrated care is further defined as being comprehensive, coordinated, and continuous. The definition states that primary care clinicians have the appropriate training to manage most problems that afflict patients (including physical, mental, emotional, and social concerns) and to involve other practitioners for further evaluation or treatment when appropriate (2). Using data from the National Ambulatory Medical Care Surveys, physician specialty groups were analyzed in a study to determine how well these Institute of Medicine primary care definitions applied to the care delivered by each specialty (3). In this analysis, obstetrics and gynecology as a specialty demonstrated some characteristics of primary care that applied to the traditional specialties of internal medicine, family and general physicians, and pediatrics. As a category, however, obstetrics and gynecology was more closely related to medical and surgical subspecialties (3). This analysis would be accepted by many practicing obstetrician-gynecologists who state that the specialty provides both primary and specialty care.

The Institute of Medicine definition includes referral, coordination, and follow-up care, but specifically does not include the function of "gatekeeper" as essential for a primary care

clinician. The emphasis placed by health maintenance organizations on limiting access to specialist physicians through the use of a "gatekeeper" primary care clinician has declined over recent years as women have strongly supported direct access to obstetrician-gynecologists and patient rights' legislation has evolved accordingly (4,5).

In recent years, there has been increasing emphasis on women's health and gender-specific medicine. Physicians have become more knowledgeable about the differences in pathophysiologic aspects of diseases in women compared with men and thus better equipped to manage them. An example is an increasing emphasis on women's cardiovascular health with preventive care and screening for risk factors.

Gynecologist as Primary Care Provider

The obstetrician-gynecologist frequently serves as a primary medical resource for women and their families, providing information, guidance, and referrals when

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appropriate. Routine health care assessments for healthy women are based on age groups and risk factors. Health guidance takes into account the leading causes of morbidity and mortality within different age groups. Patient counseling and education require an ability to assess individual needs, and to use good communication skills to encourage behavioral changes and ongoing care (1). A team approach to care is frequently helpful, utilizing the expertise of medical colleagues, such as nurses; advanced practice nurses, such as nurse midwives and nurse practitioners; health educators; other allied health professionals, such as dietitians or physical therapists; relevant social services; and other physician specialists. All clinicians, regardless of the extent of their training, have limitations to their knowledge and skills and should seek consultation at appropriate times for the benefit of their patients in providing both reproductive and nonreproductive care (1).

The National Ambulatory Care Surveys from the Centers for Disease Control and Prevention include obstetrician-gynecologists among primary care specialties as opposed to medical or surgical subspecialty (6). **Obstetrician-gynecologists provide most of general medical examinations for women of reproductive age (7). This fact indicates that obstetricians-gynecologists may already serve as the primary physicians for many of their patients.** However, when women are asked to choose which type of physician they would select if they had only one physician for all of their general medical care, family or general medical practitioners are preferred over obstetrician-gynecologists (8).

Guidelines for primary and preventive services have been issued by a number of medical bodies: the American College of Obstetricians and Gynecologists (9,10), the American Academy of Family Physicians (11), the U.S. Preventive Services Task Force (USPSTF) (12), and the American Medical Association (13,14). The guidelines from various organizations differ somewhat in their specific details, and a national guideline clearinghouse for evidence-based clinical practice guidelines, sponsored by the Agency for Healthcare Research and Quality (AHRQ), is available to provide comparisons between guidelines for a given medical condition or intervention (15). Books specific to the provision of primary health care by obstetrician-gynecologists are now available (16,17,18,19,20,21,22).

In 1998 in the United States, there were approximately 500 million visits by women to ambulatory medical care providers. Eighteen percent of the visits (76 million) were made to gynecologists (23). Forty-six percent of ambulatory visits were made by individuals between the ages of 15 and 44 years (23). The most frequently cited reason for an office visit to an obstetrician-gynecologist by women older than 15 years of age was routine prenatal examination. The second most frequently cited reason was general medical examination. For women in this age group, obstetrician-gynecologists provided more general medical

examinations than general and family practitioners and internists combined. For women of reproductive age (15–44 years), gynecologists provided nearly 4 times as many general medical examinations than did general and family practitioners, and almost 12 times as many examinations as internists (24).

When asked to characterize the nature of an office or clinic visit, obstetrician-gynecologists may or may not identify themselves as primary care providers, depending on variables (25). Those variables may include the patient's age, pregnancy status, whether it is a new versus a return visit, the diagnosis, insurance or referral status, and even geographic practice region.

Surveys of practicing physicians who were asked to categorize themselves and the nature of their practices as that of a primary care physician, a specialist, or a consultant have found that approximately one half of obstetricians and gynecologists consider themselves to be primary care providers (24,26). Gynecologists younger than 35 years of age, those in the South Atlantic census region, and those who were paid by hospitals and medical centers may be more likely to consider themselves primary care providers.

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Although not all obstetricians and gynecologists would describe themselves as being interested in serving as a primary care physician, one survey found that most considered themselves capable of serving as primary care gatekeepers without extensive additional training (27). In a 1995 survey of those completing their residencies, 87% of the respondents believed that obstetrics and gynecology was primary care, and 85% planned to practice accordingly after residency (28). However, only one half of residency training directors supported the inclusion of 6 months of primary care in the residency education program (29).

Recent changes in the Residency Review Committee's (RRC) requirements for primary care training in obstetrics and gynecology focus on the integration of primary care training throughout the 4-year residency program. Residency review committee requirements call for a focus on reproductive health care and ambulatory primary health care for women, including health maintenance, disease prevention, diagnosis, treatment, consultation, and referral (30).

Obstetricians-gynecologists are less likely than other primary care physicians to refer their patients to other specialists. Data compiled by the National Center for Health Statistics (NCHS) indicate that gynecologists had a referral rate of 4%, general internists 7.3%, and family and general practitioners 7.3% (31). Although obstetricians-gynecologists frequently do provide preventive care and guidance, there is room for improvement in these aspects of care. Obstetricians-gynecologists are as likely as family physicians or those in general practice to counsel about exercise and to measure blood pressure, although somewhat less likely than other physicians to counsel about smoking cessation and weight loss or to screen for hyperlipidemia (32). Obstetrician-gynecologists, family physicians, and general physicians were all less likely than internists or cardiologists to provide these cardiovascular preventive services.

In 1993, ACOG commissioned a Gallup poll to assess how women viewed the care provided by their obstetrician-gynecologists (8). **When compared with other physicians, obstetrician-gynecologists were more likely than other physicians to perform cervical cytology testing, pelvic examination, and breast examination.**

Obstetrician-gynecologists were as likely as other physicians to have checked blood pressure and referred patients for mammography. When compared with other physicians, they were slightly less likely to have checked cholesterol levels. Obstetrician-gynecologists are somewhat more likely than other physicians to have discussed family planning, preconception issues, and STDs, including human immunodeficiency virus (HIV). Other physicians were more likely than obstetrician-gynecologists to discuss medication use. Other physicians were as likely

as obstetrician-gynecologists to have discussed diet and exercise, smoking, alcohol use, hormone replacement therapy, osteoporosis, emotional problems, illegal drug use, and physical abuse (8). More than one half of all women who reported seeing an obstetrician-gynecologist considered him or her to be their primary physician. As expected, the percentage was highest among women aged 18 to 29 years (69%) and lowest among women older than 40 years (45%) (8). Another survey of young, low-income women attending an ob-gyn clinic found that a similar percentage—nearly half—characterized the clinic as providing primary care (33).

Approaches to Preventive Care

Currently in health care, the focus is shifting from disease to prevention. Efforts are under way to promote effective screening measures that can have a beneficial effect on public and individual health. Following is a brief description of programs developed by ACOG, the USPSTF, and the American Medical Association to provide guidelines for preventive care.

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Guidelines for Primary and Preventive Care

The initial evaluation of a patient involves a complete history, physical examination, routine and indicated laboratory studies, evaluation and counseling, appropriate immunizations, and relevant interventions. Risk factors should be identified and arrangements should be made for continuing care or referral, as needed. **The leading causes of death and morbidity within different age groups are listed in** Tables 8.1 and 8.2 (34).

Table 8.1 Leading Causes of Death by Age Group

Ages 13–18 years

1. Accidents
2. Malignant neoplasms
3. Homicide
4. Suicide
5. Diseases of the heart
6. Congenital anomalies

Ages 19–39 years

1. Malignant neoplasms
2. Accidents
3. Diseases of the heart
4. Suicide
5. Human immunodeficiency virus (HIV) disease
6. Homicide

Ages 40–64 years

1. Malignant neoplasms
2. Diseases of the heart
3. Cerebrovascular diseases
4. Chronic lower respiratory disease
5. Diabetes mellitus
6. Accidents
7. Chronic liver disease and cirrhosis
8. Suicide
9. Human immunodeficiency virus (HIV) disease

Ages 65 years and older

1. Diseases of the heart
 2. Malignant neoplasms
 3. Cerebrovascular disease
 4. Chronic lower respiratory diseases
 5. Alzheimer's disease
 6. Influenza and pneumonia
 7. Diabetes mellitus
-

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Table 8.2 Leading Causes of Morbidity by Age Group

<i>Ages 13–18 years</i>	<i>Ages 40–64 years</i>
Acne	Arthritis or osteoarthritis
Asthma	Asthma
Chlamydia	Back symptoms
Diabetes mellitus	Cancer
Headache	Cardiovascular disease
Infective, viral, and parasitic diseases	Depression
Mental disorders, including affective and neurotic disorders	Diabetes mellitus
Nose, throat, ear, and upper respiratory infections	Headache/migraine
Sexual assault	Hypertension
Sexually transmitted diseases	Menopause
Urinary tract infections	Mental disorders, including affective and neurotic disorders
Vaginitis	Mononeuritis of upper limb and mononeuritis multiples
<i>Ages 19–39 years</i>	Nose, throat, ear, and upper respiratory infections
Acne	Obesity
Appendicitis	Pneumonia
Arthritis	Sexually transmitted diseases
Asthma	Skin conditions/dermatitis
Back symptoms	Ulcers
Cancer	Urinary tract infections
Chlamydia	Vision impairment

Depression	<i>Ages 65 years and older</i>
Diabetes mellitus	Arthritis or osteoarthritis
Gynecologic disorders	Asthma
Headache/migraine	Back symptoms
Hypertension	Cancer
Infective, viral, and parasitic diseases	Cardiovascular disease
Joint disorders	Chronic obstructive pulmonary diseases
Menstrual disorders	Diabetes mellitus
Mental disorders, including affective and neurotic disorders	Hearing and vision impairment
Nose, throat, ear, and upper respiratory infections	Hypertension
Obesity	Mental disorders, including affective and neurotic disorders
Sexual assault/domestic violence	Nose, throat, ear, and upper respiratory infections
Sexually transmitted diseases	Obesity
Skin rash/dermatitis	Osteoporosis
Substance abuse	Pneumonia
Urinary tract infections	Septicemia
	Skin lesions/dermatoses/dermatitis
	Ulcers
	Urinary tract infections
	Urinary tract (other conditions, including urinary incontinence)
	Vertigo

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Subsequent care should follow a specific schedule, yearly or as appropriate based on the patient's needs and age. The ACOG recommendations for periodic evaluation, screening, and counseling by age groups are shown in Tables 8.3, 8.4, 8.5, 8.6. These tables also include recommendations for patients who have high-risk factors that require targeted screening or treatment; patients should be made aware of any high-risk conditions that require more specific screening or treatment (35). High-risk factors are listed in Table 8.7. Recommendations for immunizations are included in Table 8.8.

Guide to Clinical Preventive Services

The USPSTF, originally commissioned in 1984, was a 20-member nongovernmental panel of experts in primary care medicine, epidemiology, and public health. Initial and subsequent reviews and recommendations are being revised and periodically released on the Web site sponsored by the AHRQ (12). The charge to the panel was to develop recommendations for the appropriate use of preventive interventions based on a systematic review of evidence of

clinical effectiveness. The panel was asked to rigorously evaluate clinical research to assess the merits of preventive measures, including screening tests, counseling, immunizations, and medications.

The task force uses systematic reviews of the evidence on specific topics in clinical prevention that serve as the scientific basis for recommendations. The task force reviews the evidence, estimates the magnitude of benefits and harms, reaches consensus about the net benefit of a given preventive service, and issues a recommendation. The task force grades the quality of the evidence as good, fair, or poor, and then issues a recommendation varying from strongly recommends to recommends against, or concludes that there is insufficient evidence to recommend for or against an intervention (35) (Table 8.9). The task force reviewed only those preventive services that would be provided for asymptomatic individuals.

Primary preventive measures are those that involve intervention before the disease develops, for example, quitting smoking, increasing physical activity, eating a healthy diet, quitting alcohol and other drug use, using seat belts, and receiving immunizations. Secondary preventive measures are those used to identify and treat asymptomatic persons who have risk factors or preclinical disease but in whom the disease itself has not become clinically apparent. Examples of secondary preventive measures are well known in gynecology, such as screening mammography and cervical cytology testing.

The USPSTF is supported by an Evidence-based Practice Center (EPC), which conducts systematic reviews of the evidence that serve as the scientific basis for USPSTF recommendations. These reviews analyze the effectiveness of various screening measures and tests. Preventive medicine and the discipline of evidence-based medicine have grown and evolved since the release of the first *Guide to Clinical and Preventive Services* in 1989 (36).

Table 8.3 Periodic Assessment Ages 13–18 Years

<i>Screening</i>	<i>Evaluation and Counseling</i>
History	Sexuality
Reason for visit	Development
Health status: medical, surgical, family	High-risk behaviors
Dietary/nutrition assessment	Preventing unwanted/unintended pregnancy
Physical activity	—Postponing sexual involvement
Use of complementary and alternative medicine	—Contraceptive options
Tobacco, alcohol, other drug use	Sexually transmitted diseases
Abuse/neglect	—Partner selection
Sexual practices	—Barrier protection
Physical examination	Fitness and nutrition
Height	Dietary/nutrition assessment (including eating disorders)
Weight	Exercise: discussion of program
Blood pressure	Folic acid supplementation (0.4 mg/d)
Secondary sexual characteristics (Tanner staging)	Calcium intake
Pelvic examination (when indicated by the medical history)	Psychosocial evaluation
Skin ^a	Interpersonal/family relationships
Laboratory testing	Sexual identity
Periodic	Personal goal development

Cervical cytology (annual beginning at approximately 3 years after initiation of sexual intercourse)	Behavioral/learning disorders
High-risk groups^a	Abuse/neglect
Hemoglobin level assessment	Satisfactory school experience
Bacteriuria testing	Peer relationships
Sexually transmitted disease testing	Cardiovascular risk factors
Human immunodeficiency virus (HIV) testing	Family history
Genetic testing/counseling	Hypertension
Rubella titer assessment	Dyslipidemia
Tuberculosis skin testing	Obesity
Lipid profile assessment	Diabetes mellitus
Fasting glucose testing	Health/risk behaviors
Hepatitis C virus testing	Hygiene (including dental); fluoride supplementation
Colorectal cancer screening ^b	Injury prevention
	—Safety belts and helmets
	—Recreational hazards
	—Firearms
	—Hearing
	Skin exposure to ultraviolet rays
	Suicide: depressive symptoms
	Tobacco, alcohol, other drug use

^a See Table 8.7.

^b Only for those with a family history of familial adenomatous polyposis or 8 years after the start of pancolitis. For a more detailed discussion of colorectal cancer screening, see **Smith RA, von Eschenbach AC, Vender R, et al.** American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: Update 2001—testing for early lung cancer detection [published erratum appears in *CA Cancer J Clin* 2001;51:150]. *CA Cancer J Clin* 2001;51:38–75; quiz 77–80. From **American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice.** Primary and preventive care: periodic assessments. Committee Opinion No. 292. Washington, DC: American College of Obstetricians and Gynecologists, 2003, with permission.

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This document accelerated the trend to replace consensus or expert opinion in clinical recommendations with a more systematic and explicit review of the evidence. Although evidence-based guidelines have become widely accepted, current recommendations are based on what has been described as a “*more mature appreciation of their limitations*,” including the recognition that evidence is lacking for much of medical practice, that waiting for better data from controlled trials is unrealistic, and that evidence-based guidelines could potentially cause unintended harm to patients, clinicians, and the health care system (38).

International efforts to categorize the effectiveness of treatments include the Cochrane Library, which produces and disseminates high-quality systematic reviews of health care interventions. These reviews and abstracts are published quarterly and are available online and on CD-ROM by subscription (39). The Cochrane Library

provides searchable databases online and through institutional purchase of licenses. Evidence-based guidelines are published in journals available in print and online by discipline (i.e., medicine, mental health, and nursing). Another source of evidence-based information is *Clinical Evidence*, a subscription service published by the *British Medical Journal* in print and electronic versions (online, CD-ROM, and PDA) (40). This service summarizes the current state of knowledge and uncertainty about prevention and treatment, rating treatments as beneficial, likely to be beneficial, of unknown effectiveness, likely to be ineffective or harmful, unlikely to be beneficial, or a trade-off between benefits and harms. The advantages of Web-based sites are the ease of updating and the availability of evidence to clinicians in clinical practice sites. Other Web sites that provide tools and information about evidence-based health care include the Oxford-Centre for Evidence-Based Medicine (41), the Database of Abstracts of Reviews of Effects (DARE) (42), and the American College of Physicians (ACP) Journal Club (43).

Guidelines for Adolescent Preventive Services

Around the same time that clinicians were evaluating the primary health care needs of adults, clinicians who practice adolescent medicine (with backgrounds in pediatrics, internal medicine, family medicine, gynecology, nursing, psychology, nutrition, and other professions) recognized that the guidelines for adult and pediatric health services did not always fit the needs and health risks of adolescence. Neither the ACOG Guidelines for Primary Preventive Care (9) nor the USPSTF recommendations (12) is sufficiently comprehensive or focused on this age group, although both documents include many important aspects of adolescent health care. The American Medical Association, with the assistance of a national scientific advisory board, developed the Guidelines for Adolescent Preventive Services (GAPS) in response to this perceived need for recommendations for delivering comprehensive adolescent preventive services (13,14).

Obstetrician-gynecologists typically see adolescents in crisis to provide care for unintended pregnancies or STDs, including pelvic inflammatory disease. The need for preventing these crises is evident. The GAPS report extends the framework of services provided to adolescents. The impetus for developing GAPS was the belief that a fundamental

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change in the delivery of adolescent health services was necessary. Gynecologists could easily provide most, if not all, of the recommended services; annual preventive visits to a gynecologist might well lead to the prevention of gynecologic health problems. There are numerous opportunities for primary preventive care of adolescents in a gynecologist's office.

Table 8.4 Periodic Assessment Ages 19–39 Years

<i>Screening</i>	<i>Evaluation and Counseling</i>
History	Sexuality
Reason for visit	High-risk behaviors
Health status: medical, surgical, family	Contraceptive options for prevention of unwanted pregnancy, including emergency contraception
Dietary/nutrition assessment	Preconceptional and genetic counseling for desired pregnancy
Physical activity	Sexually transmitted diseases
Use of complementary and alternative medicine	—Partner selection
Tobacco, alcohol, other drug use	—Barrier protection

Abuse/neglect	Sexual function
Sexual practices	<i>Fitness and nutrition</i>
Urinary and fecal incontinence	Dietary/nutrition assessment (including eating disorders)
<i>Physical examination</i>	Exercise: discussion of program
Height	Folic acid supplementation (0.4 mg/d)
Weight	Calcium intake
Blood pressure	<i>Psychosocial evaluation</i>
Neck: adenopathy, thyroid	Interpersonal/family relationships
Breasts	Work satisfaction
Abdomen	Lifestyle/stress
Pelvic examination	Sleep disorders
Skin ^a	<i>Cardiovascular risk factors</i>
<i>Laboratory testing</i>	Family history
<i>Periodic</i>	Hypertension
Cervical cytology (annually beginning no later than age 21 years; every 2–3 years after three consecutive negative test results if age 30 years or older with no history of cervical intraepithelial neoplasia 2 or 3, immunosuppression, human immunodeficiency virus [HIV] infection, or diethylstilbestrol exposure <i>in utero</i>) ^b	Dyslipidemia
<i>High-risk groups^a</i>	Obesity
Hemoglobin level assessment	Diabetes mellitus
Bacteriuria testing	Lifestyle
Mammography	<i>Health/Risk Behaviors</i>
Fasting glucose testing	Hygiene (including dental); fluoride supplementation
Sexually transmitted disease testing	Injury prevention
Human immunodeficiency virus (HIV) testing	—Safety belts and helmets
Genetic testing/counseling	—Occupational hazards
Rubella titer assessment	—Recreational hazards
Tuberculosis skin testing	—Firearms
Lipid profile assessment	—Hearing
Thyroid-stimulating hormone screening	—Exercise and sports involvement
Hepatitis C virus testing	Breast self-examination ^c
Colorectal cancer screening	Bone density screening
	Chemoprophylaxis for breast cancer (for high-risk women aged 35 years or older) ^d
	Skin exposure to ultraviolet rays
	Suicide: depressive symptoms
	Tobacco, alcohol, other drug use

^a See Table 8.7.

^b For a more detailed discussion of cervical cytology screening, including the use of human papillomavirus DNA testing and screening after hysterectomy, see [American College of Obstetricians and Gynecologists](#). Cervical cytology screening. Practice Bulletin No. 45. *Obstet Gynecol* 2003; 102: 417–427.

^c Despite a lack of definitive data for or against breast self-examination, breast self-examination has the potential to detect palpable breast cancer and can be recommended.

^d For a more detailed discussion of risk assessment and chemoprevention therapy, see **American College of Obstetricians and Gynecologists**. Selective estrogen receptor modulators. ACOG Practice Bulletin No. 39. *Obstet Gynecol* 2002; 100: 835–843. From **American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice**. Primary and preventive care: periodic assessments. Committee Opinion No. 292. Washington, DC: American College of Obstetricians and Gynecologists, 2003, with permission.

The GAPS report includes 24 recommendations (Table 8.10). These recommendations address the delivery of health care, focus on the use of health guidance to promote the health and well-being of adolescents and their families, promote the use of screening to identify conditions that occur relatively frequently in adolescents and cause significant suffering either during adolescence or later in life, and provide guidelines for immunizations for the primary prevention of specific infectious diseases (13).

The GAPS recommendations stem from the conclusion that the current health threats to adolescents are predominantly behavioral rather than biomedical, that more of today's adolescents are involved in health behaviors with the potential for serious consequences, that adolescents are involved in health-risk behaviors at younger ages than previous generations, that many adolescents engage in multiple health-risk behaviors, and that most adolescents engage in at least some type of behavior that threatens their health and well-being (13). **Gynecologists are in a good position to detect high-risk behaviors and to determine whether multiple risk-taking behaviors exist; for example, the early initiation of sexual activity and unsafe sexual practices are associated with substance use** (43). Adolescents who are sexually active are much more likely than are adolescents who are not sexually active to have used alcohol (6.3 times greater risk), to have used drugs other than marijuana (4 times greater risk), and to have been a passenger in a motor vehicle with a driver who was using drugs (nearly 10 times greater risk) (44). Thus, by being aware of comorbidities, gynecologists can screen for these behaviors and potentially intervene before serious harmful health consequences occur.

In recognition of the role that obstetrician-gynecologists potentially could play in providing preventive services for adolescents, ACOG has issued guidelines that build on the

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GAPS recommendations (10). These guidelines suggest an initial visit (not necessarily examination) to the obstetrician-gynecologist for health guidance, screening, and the provision of preventive health care service between the ages of 13 and 15 years and subsequent annual preventive health care visits (1,10).

Table 8.5 Periodic Assessment Ages 40–64 Years

Screening	Evaluation and Counseling
History	Sexuality^c
Reason for visit	High-risk behaviors
Health status: medical, surgical, family	Contraceptive options for prevention of unwanted pregnancy, including emergency contraception
Dietary/nutrition assessment	Sexually transmitted diseases
Physical activity	—Partner selection
Use of complementary and alternative medicine	—Barrier protection
Tobacco, alcohol, other drug use	Sexual functioning
Abuse/neglect	Fitness and nutrition
Sexual practices	Dietary/nutrition assessment
Urinary and fecal incontinence	Exercise: discussion of program
Physical examination	Folic acid supplementation (0.4 mg/d until age 50 years)
Height	Calcium intake
Weight	Psychosocial evaluation
Blood pressure	Family relationships
Oral cavity	Domestic violence
Neck: adenopathy, thyroid	Work satisfaction
Breasts, axillae	Retirement planning
Abdomen	Lifestyle/stress
Pelvic examination	Sleep disorders
Skin ^a	Cardiovascular risk factors
Laboratory testing	Family history
Periodic	Hypertension
Cervical cytology (annually beginning no later than age 21 years; every 2–3 years after three consecutive negative test results if age 30 years or older with no history of cervical intraepithelial neoplasia 2 or 3, immunosuppression, human immunodeficiency virus [HIV] infection, or diethylstilbestrol exposure <i>in utero</i>) ^b	Dyslipidemia
Mammography (every 1–2 years beginning at age 40 years; yearly beginning at age 50)	
Lipid profile assessment (every 5 years beginning at age 45 years)	
Yearly fecal occult blood testing or flexible sigmoidoscopy every 5 years <i>or</i> double contrast barium enema every 5 years <i>or</i> colonoscopy every 10 years (beginning at age 50 years)	
Fasting glucose testing (every 3 years after age 45 years)	Obesity
Thyroid-stimulating hormone screening (every 5 years beginning at age 50 years)	Diabetes mellitus
High-risk groups^a	Lifestyle
Hemoglobin level assessment	Health/Risk Behaviors

Bacteriuria testing	Hygiene (including dental)
Mammography	Hormone therapy
Fasting glucose testing	Injury prevention
Sexually transmitted disease testing	—Safety belts and helmets
Bone density screening	—Occupational hazards
Human immunodeficiency virus (HIV) testing	—Recreational hazards
Genetic testing/counseling	—Exercise and sports involvement
Tuberculosis skin testing	—Firearms
Lipid profile assessment	—Hearing
Thyroid-stimulating hormone screening	Breast self-examination ^d
Hepatitis C virus testing	Chemoprophylaxis for breast cancer (for high-risk women) ^e
Colorectal cancer screening	Skin exposure to ultraviolet rays
Bone density screening	Suicide: depressive symptoms
	Tobacco, alcohol, other drug use

^aSee Table 8.7.

^bFor a more detailed discussion of cervical cytology screening, including the use of human papillomavirus DNA testing and screening after hysterectomy, see **American College of Obstetricians and Gynecologists**. Cervical cytology screening. ACOG Practice Bulletin No. 45. *Obstet Gynecol* 2003; 102:417–427.

^cPreconceptional and genetic counseling are appropriate for certain women in this age group.

^dDespite a lack of definitive data for or against breast self-examination, breast self-examination has the potential to detect palpable breast cancer and can be recommended.

^eFor a more detailed discussion of risk assessment and chemoprevention therapy, see **American College of Obstetricians and Gynecologists**. Selective estrogen receptor modulators. ACOG Practice Bulletin No. 39. *Obstet Gynecol* 2002; 100:835–843.

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Counseling for Health Maintenance

During periodic assessments, patients should be counseled about preventive care based on their age and risk factors. **Obesity, smoking, and alcohol abuse are associated with preventable problems that can have major long-term impacts on health.** Thus, patients should be counseled about smoking cessation and moderation in alcohol use and directed to appropriate community resources as necessary. Positive health behaviors, such as eating a healthy diet and engaging in regular exercise, should be reinforced. Adjustments may be necessary based on the presence of risk factors and the woman's current lifestyle and condition. Efforts should focus on weight control, cardiovascular fitness, and reduction of risk factors associated with cardiovascular disease and diabetes (1,45,46,47,48).

Nutrition

Patients should be given general nutritional information and referred to other professionals if they have special needs (47). **Assessment of the patient's body mass index (weight [in kilograms] divided by height [in meters] squared [kilograms per square meter])**

will give valuable information about the patient's nutritional status. Tables and methods to calculate BMI are available in print and electronic resources. Patients who are

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20% above or below the normal range require evaluation and counseling and should be assessed for systemic disease or an eating disorder. **Of adult women in the United States, 62% are either overweight (BMI 25–29.9) or obese (BMI \geq 30); 34% are obese (49). Overweight and obesity substantially increase the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, and cancers of the endometrium, breast, and colon (50).**

Table 8.6 Periodic Assessment Ages 65 and Older	
Screening	Evaluation and Counseling
History	Sexuality^c
Reason for visit	Sexual functioning
Health status: medical, surgical, family	Sexual behaviors
Dietary/nutrition assessment	Sexually transmitted diseases
Physical activity	—Partner selection
Use of complementary and alternative medicine	—Barrier protection
Tobacco, alcohol, other drug use	Fitness and nutrition
Abuse/neglect	Dietary/nutrition assessment
Sexual practices	Exercise: discussion of program
Urinary and fecal incontinence	Calcium intake
Physical examination	Psychosocial evaluation
Height	Neglect/abuse
Weight	Lifestyle/stress
Blood pressure	Depression/sleep disorders
Oral cavity	Family relationships
Neck: adenopathy, thyroid	Work/retirement satisfaction
Breasts, axillae	Cardiovascular risk factors
Abdomen	Hypertension
Pelvic examination	Dyslipidemia
Skin ^a	Obesity
Laboratory testing	Sedentary lifestyle
Periodic	Health/Risk Behaviors
Cervical cytology (every 2–3 years after three consecutive negative test results if no history of cervical intraepithelial neoplasia 2 or 3, immunosuppression, human immunodeficiency virus [HIV] infection, or diethylstilbestrol exposure <i>in utero</i>) ^b	Hygiene (including dental)
Urinalysis	
Mammography	
Lipid profile assessment (every 5 years)	

Yearly fecal occult blood testing <i>or</i> flexible sigmoidoscopy every 5 years <i>or</i> yearly fecal occult blood testing plus flexible sigmoidoscopy every 5 years <i>or</i> double contrast barium enema every 5 years <i>or</i> colonoscopy every 10 years	
Fasting glucose testing (every 3 years after age 45 years)	Hormone therapy
Bone density screening ^c	Injury prevention
Thyroid-stimulating hormone screening (every 5 years beginning at age 50 years)	—Safety belts and helmets
High-risk groups^a	—Occupational hazards
Hemoglobin level assessment	—Recreational hazards
Sexually transmitted disease testing	—Exercise and sports involvement
Human immunodeficiency virus (HIV) testing	—Firearms
Tuberculosis skin testing	Visual acuity/glaucoma
Thyroid-stimulating hormone screening	Hearing
Hepatitis C virus testing	Breast self-examination ^d
Colorectal cancer screening	Chemoprophylaxis for breast cancer (for high-risk women) ^e
	Skin exposure to ultraviolet rays
	Suicide: depressive symptoms
	Tobacco, alcohol, other drug use

^aSee Table 8.7.

^bFor a more detailed discussion of cervical cytology screening, including the use of human papillomavirus DNA testing and screening after hysterectomy, see **American College of Obstetricians and Gynecologists**. Cervical cytology screening. ACOG Practice Bulletin No. 45. *Obstet Gynecol* 2003;102:417–427.

^cPreconceptional and genetic counseling are appropriate for certain women in this age group.

^dDespite a lack of definitive data for or against breast self-examination, breast self-examination has the potential to detect palpable breast cancer and can be recommended.

^eFor a more detailed discussion of risk assessment and chemoprevention therapy, see American College of Obstetricians and Gynecologists. Selective estrogen receptor modulators. ACOG Practice Bulletin No. 39. *Obstet Gynecol* 2002;100:835–843. From **American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice**. Primary and preventive care: periodic assessments. Committee Opinion No. 292. Washington, DC: American College of Obstetricians and Gynecologists, 2003; with permission.

Central obesity—measured as waist-to-hip ratio—is an independent risk factor for disease. Women with a waist circumference greater than 35 inches are at higher risk of diabetes, dyslipidemia, hypertension, and cardiovascular disease (51).

Key nutritional recommendations have been issued by the Dietary Guidelines Advisory Committee to the U.S. Department of Agriculture (52). These recommendations are included in the new Food Guide Pyramid, which has been revised and individualized with an emphasis on whole grains, fruits, and vegetables (Fig. 8.1). The pyramid is based on the need to eat a variety of foods to get adequate energy, protein, vitamins, minerals, and fiber (52,53). It includes lean meats, poultry, fish, beans, eggs, and nuts, and is low in saturated fats, trans

fats, cholesterol, salt, and added sugars. The new pyramid recognizes the need to balance food and physical activity.

Fiber content of the diet is being studied for its potential role in the prevention of several disorders, particularly colon cancer. Currently, it is recommended that the average diet for women contain 25 g of fiber per day (53). Whole-grain foods, as well as vegetables, citrus fruits, and some legumes, are high in fiber and are emphasized in the new guidelines for healthy foods.

Adequate calcium intake is important in the prevention of osteoporosis. A postmenopausal woman should ingest 1,500 mg/day. Adolescents require 1,300 mg/day. There is no evidence that moderate caffeine intake causes osteoporosis when calcium intake is adequate. Because it is difficult to ingest an adequate amount of calcium daily in an average diet, supplements may be required.

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Table 8.7 High-Risk Factors	
<i>Intervention</i>	High-Risk Factor
Bacteriuria testing	Diabetes mellitus
Bone density screening^a	Postmenopausal women younger than 65 years: personal history of fracture as an adult; history of fracture in a first-degree relative; Caucasian; dementia; poor health or frailty; current cigarette smoking; low body weight (<127 lb); estrogen deficiency caused by early (age <45) menopause, bilateral ovariectomy, or prolonged (>1 year) premenopausal amenorrhea; low lifelong calcium intake; alcoholism; impaired eyesight despite adequate correction; recurrent falls; inadequate physical activity. All women: certain diseases or medical conditions and those who take certain drugs associated with an increased risk of osteoporosis
Colorectal cancer screening^b	Colorectal cancer or adenomatous polyps in first-degree relative younger than 60 years or in two or more first-degree relatives of any ages; family history of familial adenomatous polyposis or hereditary nonpolyposis colon cancer; history of colorectal cancer, adenomatous polyps, inflammatory bowel disease, chronic ulcerative colitis, or Crohn's disease
Fasting glucose testing	Overweight (body mass index ≥ 25 kg/m ²); family history of diabetes mellitus; habitual physical inactivity; high-risk race/ethnicity (e.g., African American, Hispanic, Native American, Asian, Pacific Islander); have given birth to a newborn weighing more than 9 lb or history of gestational diabetes mellitus; hypertension; high-density lipoprotein cholesterol level of at ≤ 35 mg/dL; triglyceride level of at ≥ 250 mg/dL; history of impaired glucose tolerance or impaired fasting glucose; polycystic ovary syndrome; history of vascular disease

Fluoride supplementation	Live in area with inadequate water fluoridation (<0.7 ppm)
Genetic testing/counseling	Considering pregnancy and: will be age 35 or older; patient, partner, or family member with history of genetic disorder or birth defect; exposure to teratogens; or African, Acadian, European Caucasian, Eastern European (Ashkenazi) Jewish, Mediterranean, or Southeast Asian ancestry
Hemoglobin level assessment	Caribbean, Latin American, Asian, Mediterranean, or African ancestry; history of excessive menstrual flow
HAV vaccination	Chronic liver disease; clotting factor disorders; illegal drug users; individuals who work with HAV-infected nonhuman primates or with HAV in a research laboratory setting; individuals traveling to or working in countries that have high or intermediate endemicity of hepatitis A
HBV vaccination	Hemodialysis patients; patients who receive clotting factor concentrates; health care workers and public safety workers who have exposure to blood in the workplace; individuals in training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions; injecting drug users; individuals with more than one sexual partner in the previous 6 months; individuals with a recently acquired STD; all clients in STD clinics; household contacts and sexual partners of individuals with chronic HBV infection; clients and staff of institutions for the developmentally disabled; international travelers who will be in countries with high or intermediate prevalence of chronic HBV infection for more than 6 months; inmates of correctional facilities
HCV testing	History of injecting illegal drugs; recipients of clotting factor concentrates before 1987; chronic (long-term) hemodialysis; persistently abnormal alanine aminotransferase levels; recipient of blood from a donor who later tested positive for HCV infection; recipient of blood or blood-component transfusion or organ transplant before July 1992; occupational percutaneous or mucosal exposure to HCV-positive blood
HIV testing	Seeking treatment for STDs; drug use by injection; history of prostitution; past or present sexual partner who is HIV positive or bisexual or injects drugs; long-term residence or birth in an area with high prevalence of HIV infection; history of transfusion from 1978 to 1985; invasive cervical cancer; pregnancy. Offer to women seeking preconception evaluation.

Influenza vaccination	Anyone who wishes to reduce the chance of becoming ill with influenza; chronic cardiovascular or pulmonary disorders, including asthma; chronic metabolic diseases, including diabetes mellitus, renal dysfunction, hemoglobinopathies, and immunosuppression (including immunosuppression caused by medications or by HIV); residents of nursing homes and other long-term care facilities; individuals likely to transmit influenza to high-risk individuals (e.g., household members and caregivers of elderly, those with medical indications, and adults with high-risk conditions); health care workers; daycare workers
Lipid profile assessment	Family history suggestive of hyperlipidemia; family history of premature (age <50 years for men, age <60 years for women) cardiovascular disease; diabetes mellitus; multiple coronary heart disease risk factors (e.g., tobacco use, hypertension)
Mammography	Women who have had breast cancer or who have a first-degree relative (i.e., mother, sister, or daughter) or multiple other relatives who have a history of premenopausal breast or breast and ovarian cancer
MMR vaccination	Adults born in 1957 or later should be offered vaccination (1 dose of MMR) if there is no proof of immunity or documentation of a dose given after first birthday; persons vaccinated in 1963–1967 should be offered revaccination (2 doses); health care workers, students entering college, international travelers, and rubella-negative postpartum patients should be offered a second dose.
Pneumococcal vaccination	Chronic illness, such as cardiovascular disease, pulmonary disease, diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid leaks, functional asplenia (e.g., sickle cell disease) or splenectomy; exposure to an environment where pneumococcal outbreaks have occurred; immunocompromised patients (e.g., HIV infection, hematologic or solid malignancies, chemotherapy, steroid therapy. Revaccination after 5 years may be appropriate for certain high-risk groups.
Rubella titer assessment	Childbearing age and no evidence of immunity
STD testing	History of multiple sexual partners or a sexual partner with multiple contacts; sexual contact with individuals with culture-proven STD, history of repeated episodes of STDs, attendance at clinics for STDs, routine screening for chlamydial infection for all sexually women aged 25 years or younger and other asymptomatic women at high risk for infection; routine screening for gonorrheal infection for all sexually active adolescents and other asymptomatic women at high risk for infection

Skin examination	Increased recreational or occupational exposure to sunlight; family or personal history of skin cancer; clinical evidence of precursor lesions
Thyroid-stimulating hormone screening	Strong family history of thyroid disease; autoimmune disease (evidence of subclinical hypothyroidism may be related to unfavorable lipid profiles)
Tuberculosis skin testing	Human immunodeficiency virus infection; close contact with persons known or suspected to have tuberculosis; medical risk factors known to increase risk of disease if infected; born in country with high tuberculosis prevalence; medically underserved; low income; alcoholism; intravenous drug use; resident of long-term care facility (e.g., correctional institutions, mental institutions, nursing homes and facilities); health professional working in high-risk health care facilities
Varicella vaccination	All susceptible adults and adolescents, including health-care workers; household contacts of immunocompromised individuals; teachers; day-care workers; residents and staff of institutional settings, colleges, prisons, or military installations; adolescents and adults living in households with children; international travelers; nonpregnant women of childbearing age

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus, HIV, human immunodeficiency virus; MMR, measles-mumps-rubella; STD, sexually transmitted diseases.

^aFor a more detailed discussion of bone density screening, see **American College of Obstetricians and Gynecologists**. Bone density screening for osteoporosis. Committee Opinion No. 270, *Obstet Gynecol* 2002;99:523–525.

^bFor a more detailed discussion of colorectal cancer screening, see **Smith RA, von Eschenbach AC, Vender R, et al**. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001—testing for early lung cancer detection [published erratum appears in *CA Cancer J Clin* 2001;51:150]. *CA Cancer J Clin* 2001;51:38–75; quiz 77–80.

From **American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice**. Primary and preventive care: periodic assessments. Committee Opinion No. 292. Washington, DC: American College of Obstetricians and Gynecologists, 2003, with permission.

Table 8.8 Immunizations

<i>Ages 13–18 Years</i>	<i>Ages 19–39 Years</i>	<i>Ages 40–64 Years</i>	<i>Age 65 Years and Older</i>
Periodic			
<ul style="list-style-type: none"> • Tetanus-diphtheria booster (once between ages 11 years and 16 years) • Hepatitis B virus vaccine (one series for those not previously immunized) 	<ul style="list-style-type: none"> • Tetanus-diphtheria booster (every 10 years) 	<ul style="list-style-type: none"> • Influenza vaccine (annually beginning at age 50 years) • Tetanus-diphtheria booster (every 10 years) 	<ul style="list-style-type: none"> • Tetanus-diphtheria booster (every 10 years) • Influenza vaccine (annually) • Pneumococcal vaccine (once)
High-risk groups^a			
Influenza vaccine	Measles-mumps-rubella vaccine	Measles-mumps-rubella vaccine	Hepatitis A vaccine
Hepatitis A vaccine	Hepatitis A vaccine	Hepatitis A vaccine	Hepatitis B vaccine
Pneumococcal vaccine	Hepatitis B vaccine	Hepatitis B vaccine	Varicella vaccine
Measles-mumps-rubella vaccine	Influenza vaccine	Influenza vaccine	
Varicella vaccine	Pneumococcal vaccine Varicella vaccine	Pneumococcal vaccine Varicella vaccine	
<p>^aSee Table 8.7. From American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice. Primary and preventive care: periodic assessments. Committee Opinion No. 292. Washington, DC: American College of Obstetricians and Gynecologists, 2003, with permission.</p>			

The Centers for Disease Control and Prevention has recommended that women of reproductive age who are capable of becoming pregnant take supplemental folic acid (0.4 mg daily) to help prevent neural tube defects in their infants (54). Women who are contemplating pregnancy should be counseled about the risk of fetal neural tube defects and the role of folic acid in their prevention.

Alcohol

Alcoholic beverages should be limited to one drink per day for women (52). A simple device called the T-ACE questionnaire can be used to elicit information about alcohol use and identify problem drinkers (Table 8.11). Women should be questioned in a nonjudgmental fashion about their alcohol use and directed to counseling services as required.

Exercise

Exercise can help control or prevent hypertension, diabetes mellitus, hypercholesterolemia, and cardiovascular disease and helps to promote overall good health, psychological well-being, and a healthy body weight. Moderate exercise along with calcium supplementation can help retard bone loss in postmenopausal women (55,56). During early menopause, weight-bearing exercise alone is not sufficient to prevent bone loss, although it will slow the rate of bone loss (55). Exercise

helps promote weight loss, strength and fitness, and stress reduction. Federal exercise guidelines released with dietary guidelines in 2005 from the Department of Health and Human Services recommend "at least 30 minutes of moderate-intensity physical activity, above usual activity, at work or home on most days of the week" to reduce the risk of chronic disease in adulthood (52). The guidelines encourage physical activity of more vigorous intensity or longer duration to provide greater health benefits for most people. "Approximately 60 minutes of moderate- to vigorous-intensity activity on most days of the week" are recommended, coupled with adherence to caloric intake requirements,

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to help manage body weight and prevent "gradual, unhealthy body weight gain in adulthood." **To sustain weight loss in adulthood, 60 to 90 minutes of daily moderate-intensity physical activity are recommended** (52). Cardiovascular conditioning, stretching exercises for flexibility, and resistance exercises or calisthenics for muscle strength and endurance are recommended for most people (52). Before beginning an exercise program, patients should be examined to ensure that exercise will not pose a risk to their health. Women should be counseled about safety guidelines for exercise. Factors that should be considered in establishing an exercise program include medical limitations, such as obesity or arthritis, and selection of activities that promote health and enhance compliance (48). **High-impact exercise is not necessary to achieve benefits, and it may be harmful. Regular low-impact or moderate aerobic exercise has been associated with improved long-term compliance and adequate health maintenance benefits.**

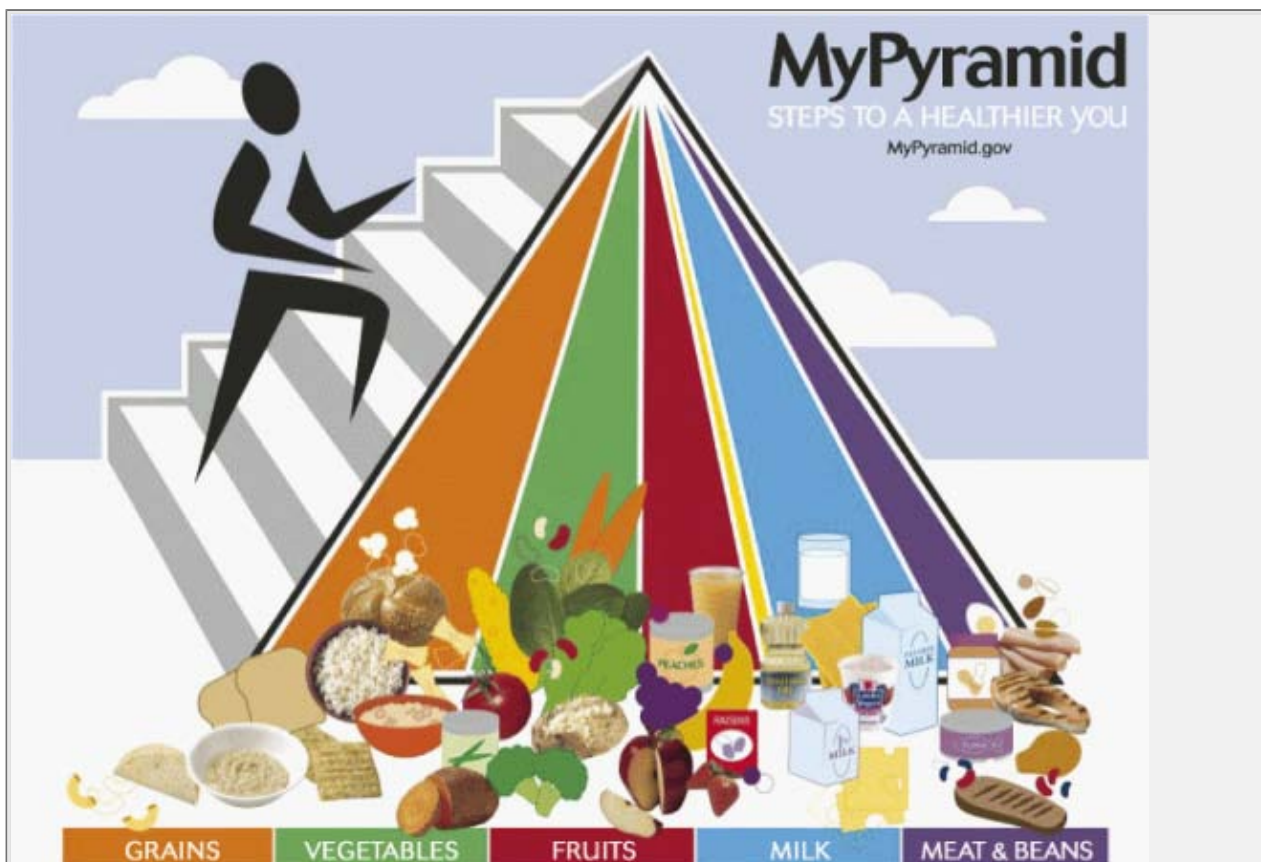


Figure 8.1 My Pyramid. This is a guide to help men and nonpregnant women choose foods that will give them the nutrients they need. The pyramid allows customization for women, age, and level of physical activity. (From U.S. Department of Agriculture and the U.S. Department of Health and Human Services, <http://www.mypyramid.com>)

Cardiovascular fitness can be evaluated by measurement of heart rate during exercise.

As conditioning improves, the heart rate stabilizes at a fixed level. The heart rate at which conditioning will develop is called the target heart rate (48). **The formula for calculating the target heart rate is 220 minus the patient's age times 0.75.** For example, a 50-year-old woman would target her heart rate at 119 ($220 - 50 = 170 = 0.75 = 119$).

Table 8.9 U.S. Preventive Services Task Force Ratings

Strength of Recommendations

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A	The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. <i>The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.</i>
B	The USPSTF recommends that clinicians provide [this service] to eligible patients. <i>The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.</i>
C	The USPSTF makes no recommendation for or against routine provision of [the service]. <i>The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.</i>
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. <i>The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.</i>
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. <i>Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.</i>

Quality of Evidence

The USPSTF grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor)

Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Ratings: Strength of recommendations and quality of evidence. In: *Guide to clinical preventive services, periodic updates, 2000–2003*. 3rd ed. Rockville, MD: U. S. Department of Health and Human Services, Agency for Healthcare Research and Quality, 2004. <http://www.ahrq.gov/clinic/3rduspstf/ratings.htm> (35).

Smoking Cessation

Smoking is a major cause of preventable illness, and every opportunity should be taken to encourage patients who smoke to quit. Patient education about the benefits of

smoking cessation, clear advice to quit smoking, and physician support improve smoking cessation rates, although 95% of smokers who successfully quit do so on their own. Self-help materials are available from the National Cancer Institute, as well as community-based support groups and local chapters of the American Cancer Society and the American Lung Association. The American Cancer Society concludes that for most people, the best way to quit includes a combination of medication, methods to enhance behavioral changes, and emotional support (57).

The AHRQ Clinical Practice Guideline on Smoking Cessation recommends nicotine replacement therapy for all smokers except pregnant women and people with cardiovascular disease (57). The "5 A's"—**A**sk, **A**dvice, **A**ssess, **A**ssist, and **A**rrange—are designed to be used to be used with smokers who are willing to quit. The *Assist* component typically includes first-line pharmacotherapy with *bupropion* or nicotine replacement in the form of gum, inhaler, nasal spray, or patch. In addition, ongoing visits for counseling and support are essential, and may include practical counseling and assistance with problem-solving skills as well as provide social support during and after treatment. Relapse prevention

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is also important, with congratulations for any successes and encouragement to remain abstinent. Patients who use tobacco but are unwilling to quit at the time of the visit should be treated with the "5 R's" motivational intervention: **R**elevance, **R**isks, **R**ewards, **R**oadblocks, and **R**epetition (57).

Table 8.10 Guidelines for Adolescent Preventive Services

I. Recommendations for Delivery of Health Services

1. From ages 11 to 21 years, all adolescents should have an annual routine health visit.
2. Preventive services should be age and developmentally appropriate, and they should be sensitive to individual and sociocultural differences.
3. Physicians should establish office policies regarding confidential care for adolescents and how parents will be involved in that care. These policies should be made clear to adolescent and the parents.

II. Recommendations for Health Guidance

4. Parents or other adult caregivers should receive health guidance at least once during their child's early adolescence, once during middle adolescence and, preferably, once during late adolescence.
5. All adolescents should receive health guidance annually to promote a better understanding of their physical growth, psychosocial and psychosexual development, and the importance of becoming actively involved in decisions regarding their health care.
6. All adolescents should receive health guidance annually to promote the reduction of injuries.
7. All adolescents should receive health guidance annually about dietary habits, including the benefits of a healthy diet, and ways to achieve a healthy diet and safe weight management.
8. All adolescents should receive health guidance annually about the benefits of physical activity and should be encouraged to engage in safe physical activity on a regular basis.
9. All adolescents should receive health guidance annually regarding responsible sexual behaviors, including abstinence. Latex condoms to prevent STDs, including HIV infection and appropriate methods of birth control, should be made available, as should instructions on how to use them effectively.

10. All adolescents should receive health guidance annually to promote avoidance of tobacco, alcohol, and other abusable substances, and anabolic steroids.

III. Recommendations for Screening

11. All adolescents should be screened annually for hypertension according to the protocol developed by the National Heart, Lung, and Blood Institute Second Task Force on Blood Pressure Control in Children.
12. Selected adolescents should be screened to determine their risk of developing hyperlipidemia and adult coronary heart disease following the protocol by the Expert Panel on Blood Cholesterol Levels in Children and Adolescents.
13. All adolescents should be screened annually for eating disorders and obesity by determining weight and stature, and asking about body image and dieting patterns.
14. All adolescents should be asked annually about their use of tobacco products, including cigarettes and smokeless tobacco.
15. All adolescents should be asked annually about their use of alcohol and other abusable substances, and about their use of over-the-counter or prescription drugs for nonmedical purposes, including anabolic steroids.
16. All adolescents should be asked annually about involvement in sexual behaviors that may result in unintended pregnancies and STDs, including HIV infection.
17. Sexually active adolescents should be screened for STDs.
18. Adolescents at risk for HIV infection should be offered confidential HIV screening with the ELISA and confirmatory test.
19. Female adolescents who are sexually active or any woman 18 years of age or older should be screened annually for cervical cancer by use of a Pap test.
20. All adolescents should be asked annually about behaviors or emotions that indicate recurrent or severe depression or risk of suicide.
21. All adolescents should be asked annually about a history of emotional, physical, and sexual abuse.
22. All adolescents should be asked annually about learning or school problems.
23. Adolescents should receive a tuberculin skin test if they have been exposed to active tuberculosis, have lived in a homeless shelter, have been incarcerated, have lived in or come from an area with a high prevalence of tuberculosis, or currently work in a health care setting.

IV. Recommendations for Immunizations

24. All adolescents should receive prophylactic immunizations according to the guidelines established by the federally convened Advisory Committee on Immunization Practices.

Excerpted from **Elster BA, Kuznets NJ. AMA guidelines for adolescent preventive services (GAPS): recommendations and rationale.** Baltimore, MD: Williams & Wilkins, 1994:xxix–xxxviii, with permission.

Table 8.11 T-ACE Questionnaire

Do you have a drinking problem?

Experts in treating alcohol abuse use the T-ACE questions below to help them find out whether a person has a drinking problem. These questions can also apply to other drugs.

T How many drinks does it take to make you feel high (TOLERANCE)?

A Have people ANNOYED you by criticizing your drinking?

C Have you ever felt you ought to CUT DOWN on your drinking?

E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (EYE-OPENER)?

If your answer to the tolerance questions is more than two drinks, give yourself a score of 2. If you answer yes to any of the other questions, give yourself a score of 1 each. If your total score is 2 or more, you may have a drinking problem.

From **Sokol RJ, Martier SS, Ager JW**. The T-ACE questions: practical prenatal detection of risk-drinking. *Am J Obstet Gynecol* 1989;160:865, with permission.

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9

Primary Care in Gynecology

Dayton W. Daberkow II

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- **Empiric therapy for women with pneumonia should be based on the specific patient profiles and the severity of their pneumonia. All patients with possible community-acquired pneumonia should have a chest radiograph to establish the diagnosis and the presence of complications.**
- **Most patients with hypertension will require two or more antihypertensive medications to achieve optimal blood pressure control, <140/90 or, <130/80 mm Hg for patients with diabetes or kidney disease.**
- **The newer recommendations by the National Cholesterol Education Program (Adult Treatment Panel III) in 2001 will probably result in an increase use of cholesterol-lowering drugs, including the "statins," a class of drugs that lower the cholesterol by blocking a liver enzyme necessary to produce cholesterol. These drugs have been very effective in reducing the risk of heart attacks and deaths in recent studies.**
- **Type 2 diabetes is frequently not diagnosed until complications appear,**

and approximately one third of all people with diabetes may be undiagnosed. Individuals at risk should be screened and a comprehensive plan of care initiated for those diagnosed with diabetes.

- **The sensitive thyroid-stimulating hormone (TSH) assay has become the single best screening test for hyperthyroidism and hypothyroidism. In clinical hypothyroidism, the standard treatment is *levothyroxine* replacement, which must be tailored to the individual patient.**

As health care providers for women, gynecologists have become responsible for providing care that extends beyond diseases of the reproductive organs to include much of the general medical care of their patients. Broadening the spectrum of care requires adjustments in practice, with less emphasis placed on the surgical aspects of the specialty. Early diagnosis and treatment of medical illnesses can have a major impact on a woman's health. Although timely referral is important for complex and advanced diseases, many conditions can be recognized and treated initially by gynecologists.

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Respiratory problems are the most common reasons patients seek care from a physician, so gynecologists should be aware of their pathophysiology. Cardiovascular disease has a significant impact on overall morbidity and is the main cause of death in women. Cardiovascular disease is associated with cigarette smoking, hypertension, hypercholesterolemia, and diabetes mellitus (DM). These conditions are responsive to screening, behavior modification, and control to lower risk factors. Thyroid disease is a major cause of morbidity for women. Because of the interaction of hormones and the overall effect on the endocrine system, thyroid disease can be of special significance in women. The gynecologist should provide screening and initial therapy for these conditions and assess the need for referral.

Respiratory Infections

Infections of the respiratory system can range from the common cold to life-threatening illness. Those with risk factors should be counseled about preventive measures. Vaccines against flu and pneumonia should be offered as indicated.

Sinusitis

A problem frequently encountered in women is self-diagnosed "sinus problems" (1). Many medical problems—headaches, dental pain, postnasal drainage, halitosis, and dyspepsia—may be related to sinus conditions. The sinuses are not an isolated organ, and diseases of the sinuses are often related to conditions that affect other portions of the respiratory system (i.e., the nose, bronchial tree, and lungs) (2). The entire respiratory system can be infected by one particular virus or pathogen (the sinobronchial or sinopulmonary syndrome); however, the most prominent symptoms are usually produced in one anatomic area. Therefore, during the evaluation of symptoms attributable to sinusitis, the presence of other infections should be investigated.

Multiple infectious and chemical agents or reactions to nervous, physical, emotional, or hormonal stimuli may cause an inflammatory response in the respiratory system (3). Systemic diseases such as connective tissue syndromes and malnutrition may contribute to chronic sinusitis. Environmental factors in the workplace and geographic conditions (e.g., cold and damp weather) may aggravate or accelerate the development of sinusitis. Factors

contributing to the development of sinus disease include atmospheric pollutants, allergy, tobacco smoke, skeletal deformities, dental conditions, barotrauma from scuba diving or airline travel, and neoplasms.

Most infections begin with a viral agent in the nose or nasopharynx that causes inflammation, blocking the draining ostia. The location of the symptoms varies by anatomic site of infection: maxillary sinus over the cheeks, ethmoid sinus across the nose, frontal sinus in the supraorbital area and sphenoid sinus to the vertex of the head. **Viral agents impede the sweeping motion of ciliary function in the sinus and, in combination with edema from inflammation, may lead to superinfection with bacteria.** The most common bacterial agents infecting sinuses are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Gram-negative organisms are usually limited to compromised hosts in intensive care units. Chronic sinusitis develops from either inadequate drainage or compromised local defense mechanisms. The flora usually are polymicrobial, consisting of aerobic and anaerobic organisms.

Sinus ailments frequently occur in middle-aged individuals. Acute infection is usually located in the maxillary and frontal sinuses. Classically, infection in the maxillary sinus is due to obstruction of the ostia found in the medial wall of the nose. Fever, malaise, a vague headache, and pain in the maxillary teeth are early symptoms. Reports of "fullness" in the

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face or exploding pressure behind the eyes often are elicited. Pressure and percussion over the malar areas can cause severe pain. Purulent exudates in the middle meatus of the nose or in the nasopharynx often are present. **Five clinical findings are most useful in diagnosis: (i) maxillary toothache, (ii) poor response to nasal decongestants, (iii) abnormal transillumination, (iv) colored visible purulent nasal secretions, and (v) a history of colored nasal discharge.** When four or more features are present, the likelihood of sinusitis is high, and when none is present, sinusitis is highly unlikely (4). Initial episodes of sinusitis do not require imaging studies; however, when persistent infections occur, studies and referral are indicated. Computed tomography of the sinuses has demonstrated that 90% of patients with colds have radiological evidence of sinus disease that usually will resolve in 2 to 3 weeks. Radiographic changes do not always reliably identify sinusitis secondary to bacteria. After sinus needle aspiration, only about 60% of patients with abnormal radiographic images have positive cultures (5). Unless culture samples are obtained by direct needle drainage, they are contaminated by oropharyngeal flora and are thus of no value. For this reason, therapy usually is empiric.

Broad antibiotic coverage of common aerobes and anaerobes is necessary but should be limited to patients with acute pain and purulent discharge. For acute, uncomplicated sinus infections, *amoxicillin* (500 mg three times a day) or *trimethoprim/ sulfamethoxazole* (1 tablet twice a day) remains the treatment of choice. *Amoxicillin* is inexpensive, penetrates the sinus tissues well, and can be changed to another antibiotic if symptoms haven't improved in 48 to 72 hours. If beta-lactam resistance is likely, *amoxicillin/clavulanic acid* (875 mg twice daily) or *azithromycin* (5-day course once a day) may be used. Other second-line drugs include *cefuroxime* (250 mg twice daily), *ciprofloxacin* (500 mg twice daily), *clarithromycin* (500 mg twice daily), *levofloxacin* (500 mg once a day), and *loracarbef* (400 mg twice daily). The usual treatment course is 10 to 14 days, and patients should be informed that relapses might occur if the full course of treatment isn't completed.

Systemic decongestants containing pseudoephedrine are useful in shrinking the obstructive ostia and promoting sinus drainage and ventilation. Topical decongestants should be used for no longer than 3 days because prolonged use may lead to rebound vasodilation and worsening of symptoms. Mucolytics like guaifenesin may help thin sinus secretions and promote drainage. Antihistamines should be avoided in acute sinusitis

because of their drying effects, which can lead to thickened secretions and poor drainage of the sinuses. Therapies to relieve symptoms include facial hot packs and analgesics. *Fluticasone*, a nasal steroid, may accelerate the recovery of patients with a history of chronic rhinitis or recurrent sinusitis who seek treatment of acute rhinosinusitis (6). Improvement should be apparent within 48 hours of treatment, but 10 days may be necessary for complete resolution of symptoms. When improvement is not rapid, resistance should be presumed, and other classes of antibiotics should be given. In persistent cases, referral to an otolaryngologist for sinus irrigation may be necessary.

Chronic sinusitis may result from repeated infections with inadequate drainage.

The interval between infections becomes increasingly shorter until there are

no remissions. Presenting symptoms are recurrent pain in the malar area or chronic postnasal drip. In the preantibiotic era, chronic sinusitis was the result of repeated acute sinusitis with incomplete resolution, whereas currently allergy is a more common cause. Injury of surface ciliated epithelium results in impaired removal of mucus. A vicious cycle ensues of incomplete resolution of infection, followed by reinfection, and ending with the emergence of opportunistic organisms. As mentioned previously, allergies have become an important factor in chronic sinusitis. The swelling and edema of the mucosa in conjunction with hypersecretion of mucus leads to ductal obstruction and infection. Chronic sinusitis is associated with chronic cough and laryngitis with intermittent acute infections. Treatment is directed at the underlying etiology: either allergy control or aggressive management of infections. Resistant cases require computed tomography and endoscopic

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surgery for polyp removal. Nasoantral window formation is radical surgery that occasionally is necessary.

No clinical criteria can reliably identify those patients who might benefit from

treatment with antibiotics. It is reasonable to treat women with presumed bacterial sinusitis if they have high fever, systemic toxicity, immune deficiency, or possible orbital or intracranial involvement (5). Although very rare, untreated sinus infections may have dire consequences, such as orbital cellulitis leading to orbital abscess, subperiosteal abscess formation of the facial bones, cavernous sinus thrombosis, and acute meningitis. Brain and dural abscesses also are rare; when they occur, it usually is the result of direct spread from a sinus. Computed tomography scanning is the most accurate diagnostic tool at present. The use of aggressive surgical approaches with broad-spectrum antibiotics is necessary for adequate drainage.

Otitis media

Otitis media remains primarily a disease of children, but may affect adults,

often secondary to a concurrent viral infection of the upper respiratory tract. Diagnosis in most cases reveals fluid behind the tympanic membrane. Treatment is directed to symptoms and usually involves the use of antihistamines and decongestants despite little data to support their use. Acute otitis media is usually a bacterial infection; *Streptococcus pneumoniae* and *Hemophilus influenzae* are the most common pathogens. Symptoms include acute purulent otorrhea, fever, hearing loss, and leukocytosis (7). Physical examination of the ear reveals a red, bulging, or perforated membrane. Indicated treatment is broad-spectrum antibiotics such as *amoxicillin/clavulanic acid*, *cefuroxime axetil* and *trimethoprim-sulfamethoxazole*.

Bronchitis

Acute bronchitis is an inflammatory condition of the tracheobronchial tree. Most often it

is viral in origin and occurs in winter. Common cold viruses (rhinovirus and coronavirus), adenovirus, influenza virus, and *Mycoplasma pneumoniae* (a nonviral pathogen) are the most common pathogens involved. Bacterial infections occur less commonly and may be secondary pathogens. Cough, hoarseness, and fever are the usual presenting symptoms. In the initial 3 to 4 days, the symptoms of rhinitis and sore throat are prominent; however, coughing may last as long as 3 weeks. Unfortunately, the prolonged nature of these infections promotes the use of antibiotics to "clear up the infection." Sputum production commonly occurs and may be prolonged in cigarette smokers. Most serious bacterial infections occur in cigarette smokers, who have damage to the lining of the upper respiratory tree and changes in the host flora.

Physical examination discloses a variety of upper airway sounds, usually coarse rhonchi. Rales are usually not present on auscultation, and signs of consolidation and alveolar involvement are absent. **During auscultation of the chest, signs of pneumonia such as fine rales, decreased breath sounds, and euphoria ("E to A changes") should be sought.** If the results of the physical examination are uncertain or the patient's condition appears toxic, chest radiography should be performed to detect the presence of parenchymal disease. Paradoxically, as the initial acute syndrome subsides, sputum production may become more purulent. Sputum cultures are of limited value because of the polymicrobial nature of infections. In the absence of complications, treatment is directed to relief of symptoms. The use of antibiotics is reserved for patients in whom chest radiography findings are consistent with pneumonia. Cough is usually the most aggravating symptom and may be treated with antitussive preparations containing either *dextromethorphan* or *codeine*. The efficacy of any expectorants has never been proved.

Chronic bronchitis is defined as a productive cough from excessive secretions for at least 3 months in a year for 2 consecutive years. Prevalence has been estimated to be

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between 10% and 25% of the adult population who are smokers. Previously the incidence has been lower in women than men, but as the prevalence of cigarette smoking in women has increased, so too has the incidence of bronchitis in women. Chronic bronchitis is usually classified as a form of chronic obstructive pulmonary disease (COPD, e.g., "blue bloaters"). Other causes include chronic infections and environmental pathogens found in dust. The cardinal manifestation of disease is an incessant cough, usually in the morning with expectoration of sputum. Because of frequent exacerbations and hospitalizations involved, and the complexity of medical management, these patients should be referred to an internist.

Pneumonia

Pneumonia is defined as inflammation of the distal lung that includes terminal airways, alveolar spaces, and the interstitium. Pneumonia may have multiple causes, including viral and bacterial infections or aspiration. Aspiration pneumonia is usually the result of depressed awareness commonly associated with the use of drugs and alcohol or anesthesia. Viral pneumonias are caused by multiple infectious agents, including influenza A or B, parainfluenza virus, or respiratory syncytial virus. Most viral syndromes are spread by aerosolization associated with coughing, sneezing, and even conversation. Incubation is short, requiring only 1 to 3 days before the acute onset of fever, chills, headache, fatigue, and myalgias. Symptom intensity is directly related to intensity of the host febrile reaction. Pneumonia develops in only 1% of patients who have a viral syndrome, but mortality rates may reach 30% in immunocompromised individuals and the elderly. An additional risk is the development of secondary bacterial pneumonias after the initial viral insult. These infections are more common in elderly patients and may explain the high fatality in this group (8). *Staphylococcal* pneumonias, which often arise from a previous viral infection, are

extremely lethal regardless of patient age. The best treatment for viral pneumonia is prevention by immunization. Treatment is supportive and consists mostly of administration of antipyretics and fluids.

Bacterial pneumonia is classified as either community acquired or nosocomial, and the classification determines prognosis and antibiotic therapy in many cases. Risk factors that contribute to mortality are chronic cardiopulmonary diseases, alcoholism, diabetes, renal failure, malignancy, and malnutrition. Prognostic features associated with poor outcome include greater than two lobe involvement, respiratory rate greater than 30 breaths/minute on presentation, severe hypoxemia (<60 mm Hg on room air), hypoalbuminemia, and septicemia (9). Pneumonia is a common cause of adult respiratory distress syndrome (ARDS) with a mortality rate between 50% and 70% (10).

Signs and symptoms of pneumonia vary depending on the infecting organism and the patient's immune status (11). In typical pneumonias, the usual presentation is a toxic-appearing patient with high fever, rigors, productive cough, chills, and/or pleuritic chest pain. Chest radiography often will show infiltrates. The following agents, listed in decreasing order, cause two thirds of all bacterial pneumonias: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, gram-negative organisms, and anaerobic bacteria. Atypical pneumonias are more insidious in onset than typical pneumonias. Patients have moderate fever without the characteristic rigors and chills. Additional symptoms include a nonproductive cough, headache, myalgias, and mild leukocytosis. Chest radiography reveals bronchopneumonia with a diffuse interstitial pattern; characteristically, the patient does not appear to be nearly as ill as the x-ray suggests. Common causes of atypical pneumonia include viruses, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae* (also called the TWAR agent), and other rare agents.

A strong index of suspicion is required for diagnosis, especially in elderly and immunocompromised individuals, who have altered response mechanisms. This is

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even true with "typical agents." Subtle clues in the elderly include changes in mentation, confusion, and exacerbation of other illnesses. The febrile response may be entirely absent, and the results of the physical examination are not predictable of pneumonia. Even in high-risk groups, an increased respiratory rate of greater than 25 breaths per minute remains the most reliable sign of infection. Mortality in these high-risk groups of patients is strongly correlated with the ability of the host to mount normal defenses to the symptoms of fever, chills, and tachycardia.

All women suspected of having pneumonia should undergo chest radiography to not only establish the diagnosis but also to detect alternative diagnoses such as congestive heart failure and tumors. In addition, the chest radiograph can detect complications like pleural effusions and multilobar disease. Laboratory studies helpful in identifying community-acquired pneumonia are sputum gram stain, sputum culture, and two sets of blood culture. An "adequate sputum" sample (defined as more than 25 neutrophils with less than 10 epithelial cells per low-powered field on microscopic examination) may be difficult to obtain. Respiratory therapists are an excellent resource for inducing sputum. Hospitalized patients also undergo assessment of blood-gas exchange by either oximetry or arterial blood-gas analysis. Diagnosis of *Legionella pneumophila* requires a different laboratory technique: measuring urinary antigen levels. *Mycoplasma pneumoniae* should be suspected when cold agglutinin findings are positive in the presence of the appropriate clinical symptoms.

The American Thoracic Society updated their original 1993 guidelines in 2001 (12,13). These clinical recommendations use an evidence-based approach for the diagnosis and management

of community-acquired pneumonia. Therapy should be directed at the responsible or most likely pathogen, but in many cases of pneumonia, the exact cause cannot be determined, and empiric therapy should be initiated. The American Thoracic Society recommends empiric therapy based on four groups of specific patient profiles, the presence of modifying factors (Table 9.1), and pneumonia severity.

- **Group I. Outpatients with no cardiopulmonary disease (congestive heart failure or COPD) and no modifying factors.** These patients are in the lowest-risk group and are usually infected by pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae*. Patients should be treated with an advanced generation macrolide such as *azithromycin* or *clarithromycin* or *doxycycline*.
- **Group II. Outpatients with cardiopulmonary disease and/or modifying factors.** Patients in this group usually have some comorbidities and are older than 50 years of age. Aerobic gram-negative bacilli, mixed infections with atypical pathogens, and drug-resistant *S. pneumoniae* (DRSP) should be considered in this patient population. Drug recommendations include monotherapy with an antipneumococcal fluoroquinolone, such as *gatifloxacin* or *levofloxacin*; a combination of a macrolide (or *doxycycline*) with a beta-lactam such as *cefepodoxime*, *cefuroxime*, or *amoxicillin-clavulanate*; or parenteral *ceftriaxone* followed by *cefepodoxime*.
- **Group III. Inpatients who are not in the intensive care unit and have cardiopulmonary or modifying factors.** Drugs for these patients include intravenous fluoroquinolone monotherapy or a combination of an intravenous beta-lactam agent plus either intravenous or oral administration of an advanced *macrolide* or *doxycycline*. For the small group of inpatients who don't have any cardiopulmonary diseases or modifying factors, intravenous *azithromycin* alone can be used. Alternatives include *doxycycline* plus a beta-lactam agent (if *macrolide* allergy or intolerance is present) or monotherapy with an antipneumococcal fluoroquinolone.
- **Group IV. Inpatients in the intensive care unit.** These patients usually have the most severe pneumonia, and all antibiotics are given intravenously. Immediate consultation with an internist, hospitalist, or infectious disease specialist is recommended.

Table 9.1 Modifying Factors That Increase the Risk of Infection with Specific Pathogens

Penicillin-resistant and drug resistant pneumococci

Age >65 years

Beta-lactam therapy within the past 3 months

Alcoholism

Immune-suppressive illness (including therapy with corticosteroids)

Multiple medical comorbidities

Exposure to a child in a day-care center

Enteric gram-negatives

Residence in a nursing home

Underlying cardiopulmonary disease

Multiple medical comorbidities

Recent antibiotic therapy

Pseudomonas aeruginosa

Structural lung disease (bronchiectasis)

Corticosteroid therapy (>10 mg of prednisone per day)

Broad-spectrum antibiotic therapy for >7 d in the past month

Malnutrition

Adapted from **American Thoracic Society**. Guidelines for the management of adults with community-acquired pneumonia. *Am J Respir Crit Care Med* 2001;163:1730–1754.

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Oxygen therapy and hydration should be initiated in addition to antibiotic therapy.

Most patients will have an adequate clinical response within 3 days of treatment. Oral antibiotics may be given once patients have met the following criteria: ability to eat and drink, improvement in cough and dyspnea, afebrile (<100° F) on two occasions 8 hours apart, and a decreasing white blood cell count. If other clinical features are favorable, patients may be switched to oral antibiotics even if febrile. They may also be discharged on the same day that oral antibiotics are started if other medical and social factors are favorable.

Vaccination

The **pneumococcal vaccine** should be given to people at high risk for pneumonia, which includes adults 65 years or older and people with special health problems, such as heart or lung disease, alcoholism, kidney failure, diabetes, human immunodeficiency virus (HIV) infection, or certain types of cancer. Repeat vaccination is recommended 5 years after the first dose is given. The vaccine is active against 23 types of pneumococcal strains, and most individuals develop protection within 2 to 3 weeks of inoculations.

The **influenza vaccine** should be given every fall to high-risk groups: individuals 50 years of age or older; anyone with serious long-term health problems such as heart disease, lung disease, kidney disease, diabetes, and weak immune systems as with HIV and acquired immunodeficiency syndrome (AIDS); individuals on long-term steroids or receiving cancer treatment; women who are pregnant during the flu season (November through April); and anyone coming in close contact with people at risk of serious influenza like physicians, nurses, and family members. Vaccination is best given from October to mid-November. Antiviral agents should not be used as a substitute for vaccination but may be a useful adjunct. The four agents approved for use in the United States are *amantadine*, *rimantadine*, *zanamivir*, and *oseltamivir*. These medicines

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should be given within 2 days of the onset of symptoms to shorten the duration of uncomplicated illness caused by influenza (14).

Table 9.2 Major Risk Factors for Coronary Artery Disease

Age > 55 for men and >65 for women
Family history of cardiovascular disease (men <55 y; women <65 y)
Physical inactivity
Diabetes mellitus
Cigarette smoking
Dyslipidemia
Obesity (BMI \geq 30)
Hypertension
Microalbuminuria or estimated GFR <60 mL/min

Adapted from **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)**. JAMA 2003; 289: 2560–2572.

Cardiovascular Disease

The risk factors for coronary artery disease are presented in Table 9.2. Central to treating cardiovascular disease is the control of contributing diseases and risk factors through lifestyle modifications (Table 9.3). Aerobic exercise protects against cardiovascular disease (15). Additional aspects of prevention of myocardial disease, renal disease, and stroke include control of hypertension, identification and control of diabetes and obesity, and control of dietary fats, especially cholesterol, in susceptible individuals (Fig. 9.1). The presence or absence of target organ damage shown in Table 9.4 also determines the risk of coronary artery disease in hypertensive patients.

Hypertension

The relationship between hypertension and cardiovascular events such as stroke, coronary artery disease, congestive heart disease, and renal disease is well known. More than 50 million people in the United States have hypertension. It is found in 15% of the population between the ages of 18 and 74 years; the incidence increases with age and varies with race. After age 50, women have a higher incidence of hypertension than men; however, this may be a confounding variable related to the overall mortality of men

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at an earlier age (16). More than 60% of those individuals older than age 60 years can be classified as hypertensive (17). The contribution of hypertension to overall cardiovascular morbidity and mortality in women has been thought less important than in men, but this may reflect the relative absence of research in women. Recognition and treatment of hypertension may decrease the development of renal and cardiac disease.

Table 9.3 Lifestyle Adjustments to Manage Hypertension

Weight reduction to maintain a body mass index of 18.5–24.9

Limit alcohol use to 2 drinks per day for men (24 oz beer, 10 oz of wine, 3 oz of 80-proof whiskey) and no more than 1 drink per day in women and lighter-weight persons

Regular aerobic exercise (at least 30 minutes per day of brisk walking most days of the week)

Decrease salt intake to less than 2.4 grams of sodium or 6 grams of sodium chloride per day

Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat

Adapted from **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)**. *JAMA* 2003; 289: 2560–2572.

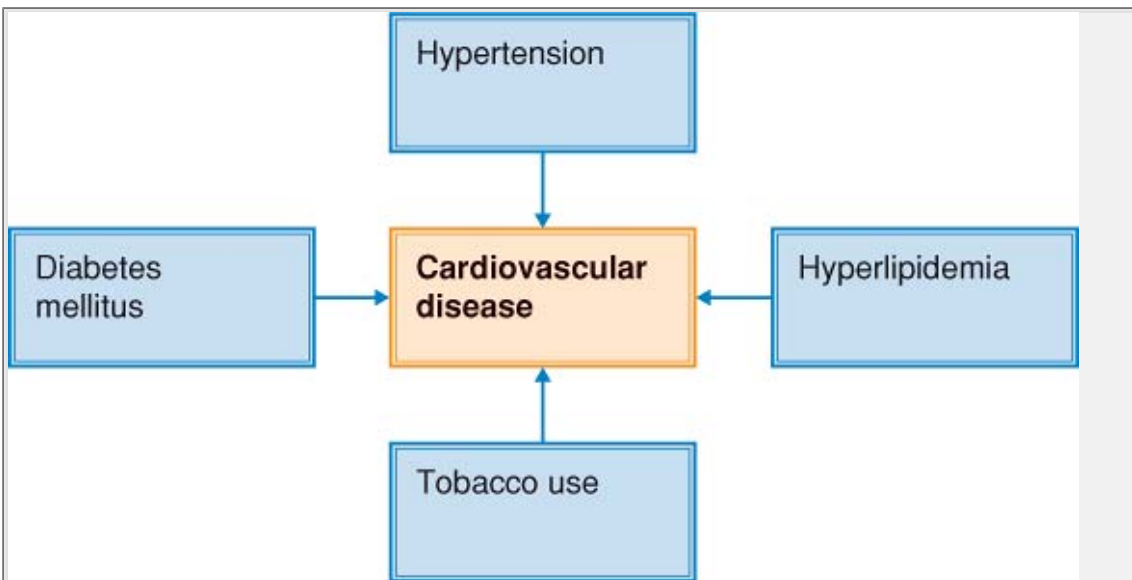


Figure 9.1 Disease and risk factors contributing to cardiovascular disease.

Epidemiology

The incidence of hypertension is twice as high in African Americans than in whites. Geographic variations also exist: The southeastern United States has a higher prevalence of hypertension and stroke, regardless of race (18). One multi-institutional study confirmed that not only is there an increased incidence of hypertension in African Americans, but also that lower levels of education increase the incidence (19). Preventive measures can be most effective in those at highest risk, such as in African-American women and individuals from the lowest socioeconomic level (19). The influence of genetic predisposition is poorly understood. Studies of women have been limited to those that determine side effects of medication and the impact of certain medications on long-term lipid status (16).

Table 9.4 Target Organ Damage

Stroke or transient ischemic attacks
Hypertensive retinopathy
Heart disease
Angina or prior myocardial infarction
Congestive heart failure
Prior coronary revascularization
Left ventricular hypertrophy
Chronic kidney disease
Peripheral arterial disease

Adapted from **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)**. *JAMA* 2003;289:2560–2572.

Table 9.5 Laboratory Tests and Procedures Recommended in the Evaluation of Uncomplicated Hypertension ^a

Urinalysis
Complete blood count
Potassium
Creatinine or estimated glomerular filtration rate
Calcium
Fasting glucose
Lipid profile that includes HDL, LDL, and triglycerides after a 9- to 12-hour fast
12-lead electrocardiogram

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aIf any of the above are abnormal, consultation or referral to an internist is indicated.

Adapted from **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)**. *JAMA* 2003;289:2560–2572.

Classically, hypertension is defined as blood pressure levels higher than 140/90 when measured on two separate occasions. Therapy, however, may be indicated only for individuals at high risk. Individuals at low risk, such as white women with no other risk factors, may benefit from lifestyle modification alone (19). In middle-age and elderly patients, elevation of systolic blood pressure was once considered innocuous: however, recent studies suggest that control of systolic blood pressure is more important than control of diastolic blood pressure (20). Middle-aged to elderly patients treated for systolic hypertension have a significant decrease in cerebral vascular accidents and coronary artery disease (21). Life insurance risk tables indicate that when blood pressure is controlled to lower than 140/90, normal survival occurs over a 10- to 20-year follow-up, regardless of sex. Current recommendations are based on sustained blood pressures higher than 140/90.

More than 95% of individuals with hypertension have primary or essential hypertension (cause unknown), whereas fewer than 5% have secondary hypertension resulting from another disorder. Key factors to be determined in the history and physical examination include presence of prior elevated readings, previous use of antihypertensive agents, a family history of cardiovascular death before age 55, and excessive alcohol and sodium. Lifestyle modification is considered important in the therapy of hypertension; thus, a detailed history of diet and physical activity should be obtained

(22). Baseline laboratory evaluations to rule out reversible causes of hypertension (secondary hypertension) are listed in Table 9.5. Diagnosis and management are based on the classification of blood pressure readings presented in Table 9.6.

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) released their seventh report in 2003. The purpose was to

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provide an evidence-based approach to the prevention and management of hypertension

(23). **Following are key points of this report:**

- **Systolic blood pressure in those older than 50 years is a more important cardiovascular risk factor than diastolic blood pressure.**
- **Beginning at 115/75 mm Hg, the risk of cardiovascular disease doubles for each increment of 20/10 mm Hg.**
- **Those who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension.**
- **Patients with prehypertension (systolic blood pressure 120–139 mm Hg or diastolic blood pressure 80–89 mm Hg) require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and cardiovascular disease.**
- **For uncomplicated hypertension, thiazide diuretic should be used in most cases for medical treatment, either alone or combined with drugs from other classes.**
- **Other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers) should be used in the presence of specific high-risk conditions (Table 9.7).**
- **Two or more antihypertensive medications are required to achieve optimal blood pressure levels (<140/90 mm Hg, or <130/80 mm Hg) for patients with diabetes or chronic kidney disease.**
- **For patients whose blood pressure is more than 20 mm Hg above the systolic blood pressure goal or more than 10 mm Hg above the diastolic blood pressure goal, initiation of therapy using two agents, one of which will be a thiazide diuretic, should be considered.**

Table 9.6 Blood Pressure Classification (Adults 18 Years and Older)

<i>Category</i>	<i>Systolic BP (mm Hg)</i>	<i>Diastolic BP (mm Hg)</i>
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	>160	or >100

Modified from the **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)**. *JAMA* 2003; 289: 2560–2572.

Table 9.7 Drug Choices for Hypertension with Compelling Indications						
<i>Compelling Indication</i>	<i>Diuretic</i>	<i>β-blocker</i>	<i>ACE inhibitor</i>	<i>ARB</i>	<i>CCB</i>	<i>Aldosterone antagonist</i>
Heart failure	[check mark]	[check mark]	[check mark]	[check mark]		[check mark]
Post-MI		[check mark]	[check mark]			[check mark]
High coronary risk	[check mark]	[check mark]	[check mark]		[check mark]	
Diabetes	[check mark]	[check mark]	[check mark]	[check mark]	[check mark]	
Chronic kidney disease	[check mark]	[check mark]	[check mark]			
Recurrent stroke prevention	[check mark]		[check mark]			

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MI, myocardial infarction.

Adapted from **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)**. *JAMA* 2003; 289: 2560–2572.

Regardless of therapy or care, hypertension will be controlled only if patients are motivated to maintain their treatment plan. If blood pressure control is not easily achieved, if the systolic blood pressure is higher than 180 mm Hg, or if the diastolic reading is higher than 110 mm Hg, referral to an internist is recommended. Referral is also indicated if secondary hypertension is suspected or evidence of end-organ damage (renal insufficiency or congestive heart failure) is present.

Measurement of Blood Pressure

An often overlooked but essential variable in evaluation of hypertension is how measurements are obtained and the need to standardize measurements (24). "White coat" or office hypertension may occur in up to 30% of patients. For patients who have repeated normal measures outside of the office, it is reasonable to use ambulatory or home monitoring devices. In most patients, office readings are all that are necessary to adequately diagnose and monitor hypertension and eliminate problems of reliability

with commercial devices and patient interpretation skills.

Blood pressure protocols for measurement should be standardized. The patient should be allowed to rest for 5 minutes in a seated position and the right arm used for measurements (for unknown reasons, the right arm has higher readings). The cuff should be applied 20 mm above the bend of the elbow and the arm positioned parallel to the floor. The cuff should be inflated to 30 mm Hg above the disappearance of the brachial pulse, or 220 mm Hg. The cuff should be deflated slowly at a rate no more than 2 mm Hg/second.

The cuff size is important, and most cuffs are marked with "normal limits" for the relative size they can accommodate. The most common clinical problem encountered is small cuffs used with obese patients, resulting in "cuff hypertension." Phase IV Korotkoff's sounds are described as the point when pulsations are muffled, whereas phase V is complete disappearance. Most experts in hypertension advocate the use of phase V Korotkoff sounds, but phase IV sounds may be used in special circumstances, with the reason documented.

The use of automated devices may help eliminate discrepancies in measurements. Regardless of the method or device used, two measurements should be obtained with less than a 10 mm Hg disparity to be judged adequate. When repeated measures are performed, there should be a 2-minute rest period between readings. Blood pressure has a diurnal pattern, so determinations preferably should be done at the same time. Ambulatory monitoring is not cost-effective in all patients, but may be used to evaluate resistance to therapy, to assess "white coat" hypertension, and to determine whether syncopal episodes are related to hypotension or episodic hypertension (25).

Therapy

Nonpharmacologic interventions or lifestyle modifications should be attempted before initiation of medication unless the systolic blood pressure exceeds 139 mm Hg or the diastolic blood pressure exceeds 89 mm Hg. Drug therapy should also be initiated for systolic blood pressure greater than 130 mm Hg or diastolic blood pressure greater than 80 mm Hg in those with diabetes or chronic renal failure. An important element in lifestyle modifications is to modify all contributors to cardiovascular disease. In obese patients, weight loss, especially in individuals with truncal and abdominal obesity, can play a significant role in the prevention of atherosclerosis (26). A loss of just 10 pounds has been reported to lower blood pressure (27). Inquiries into dietary practices should be made to eliminate excess salt in the diet, specifically certain food groups that are high in sodium, such as canned goods, snack food, pork products, and soy sauce. By reducing salt intake to 3 grams a day, British researchers estimated that mortality per year would decrease by 70,000 deaths (28). Cholesterol and fat intake in the diet should be limited. An exercise program, weight loss, and moderating alcohol intake (to no more than 2 drinks per day) contribute to overall cardiovascular health. Aerobic exercise alone may prevent hypertension in 20% to 50% of normotensive individuals (29).

The goal of therapy is for the patient to lower blood pressure into the "normal range": a systolic reading less than or equal to 120 mm Hg and a diastolic reading less than or equal to 80 mm Hg. If lifestyle modifications are not sufficient to control blood pressure, then pharmacologic intervention is indicated (Fig. 9.2).

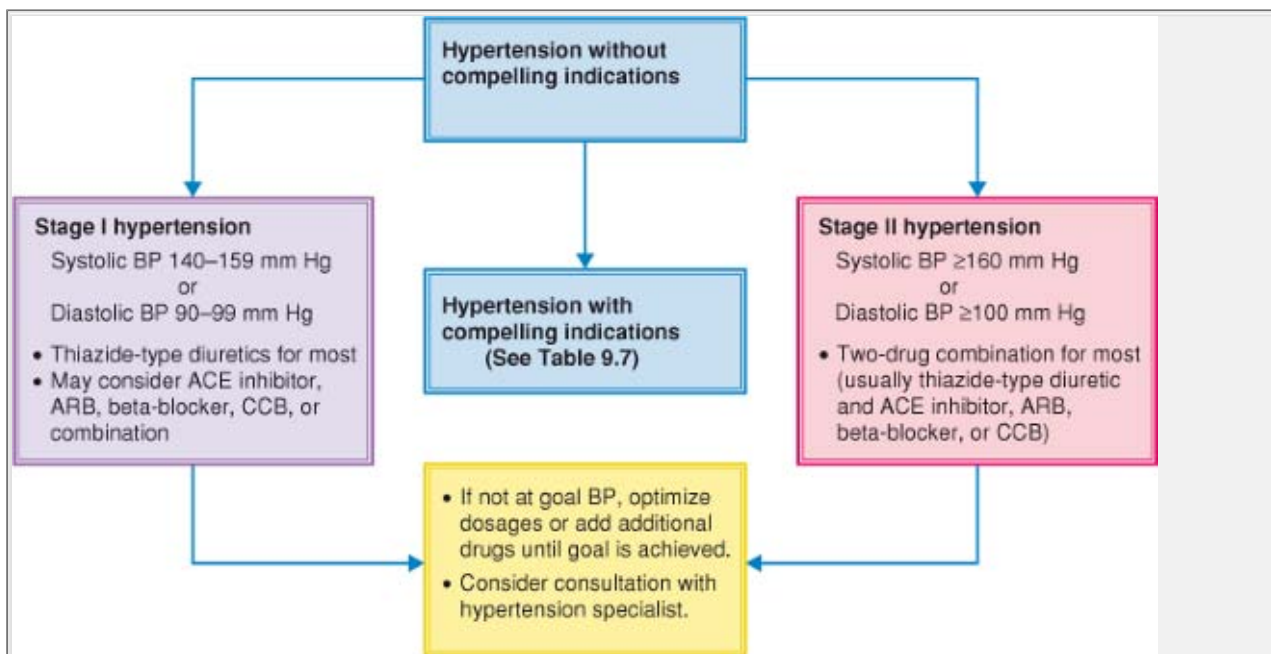


Figure 9.2 Algorithm for the drug choices for hypertensive patients unresponsive to lifestyle changes. Goal blood pressure (BP) is <140/90 mm Hg, or <130/80 mm Hg for those with diabetes or chronic kidney disease. ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker. (Modified from the **Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)**. *JAMA* 2003; 289:2560–2572, with permission.)

Diuretics

The most commonly used medication for initial blood pressure reduction is the **thiazide diuretic**. The mechanism of action is to reduce plasma and extracellular fluid volume. This lowering of volume is thought to decrease peripheral resistance. Cardiac output initially decreases and then normalizes. The important long-term effect is a slight decrease in extracellular fluid volume. The maximum therapeutic dose of thiazides should be lowered to 25 mg, rather than the commonly used 50 mg. The benefit of higher doses is eliminated by the corresponding increase in side effects. Potassium-sparing diuretics (*spironolactone*, *triamterene*, or *amiloride*) are usually available in fixed doses and should be prescribed to prevent the development of hypokalemia. Potassium supplementation is less effective than the use of potassium-sparing agents. **Thiazide diuretics are best used in patients with creatinine levels less than 2.5 g/L. Loop diuretics (*furosemide*) work better than thiazide diuretics at lower glomerular filtration rates and higher serum creatinine levels.** Control of hypertension with concurrent renal insufficiency is difficult and is probably best handled by an internist or nephrologist. Thiazides and loop diuretics should not be used concurrently because profound diuresis may occur and lead to renal impairment. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) limits the effectiveness of this class of drugs. Other side effects that further limit the usefulness of thiazide diuretics include hyperuricemia, which may contribute to acute gout attacks, glucose intolerance, and hyperlipidemias (30). The metabolic side effects of these drugs have limited their popularity recently.

Adrenergic Inhibitors

Beta-blockers have been used extensively for years as antihypertensive agents. The mechanism of action is decreasing cardiac output and plasma renin activity with some increase

in total peripheral resistance. As a class, they are an excellent source of first-line therapy, especially for migraine sufferers. The original formulation, *propranolol*, was a highly lipid soluble that contributed to bothersome side effects such as depression, sleep disturbances (nightmares in the elderly), and constipation in higher doses. *Propranolol* has a relative lack of beta selectivity, which promotes other undesirable phenomenon. Formulations such as *atenolol* are water soluble, are beta₁ selective, and have fewer side effects than *propranolol*. At higher doses, however, beta₂ effects emerge. There is no evidence to support speculation that beta₁ selective agents may be safe for use in individuals who have asthma. An additional advantage of water-soluble agents is a longer half-life. Reduced dosing schedules improve compliance. Side effects of beta-blockers include an increase in triglyceride levels and a decrease in high-density lipoprotein (HDL) cholesterol and blunting of adrenergic release in response to hypoglycemia. NSAIDs may also decrease the effectiveness of beta-blockers. Contraindications to beta-blockers are asthma, sick sinus syndrome, or bradyarrhythmia. **Beta-blockers are often used for the treatment of angina and after myocardial infarctions. However, if these drugs are acutely withdrawn, a rebound phenomenon of ischemia may occur leading to acute myocardial infarction.** Despite these potential problems, beta-blockers continue to be useful in counteracting reflex tachycardia, which often occurs with the use of smooth muscle relaxing drugs.

Use of alpha₁-adrenergic drugs became popular in men because of their minimal effects on potency and unique relationship to lipids. Interestingly, they may contribute to stress urinary incontinence in women because of altered urethral tone (31). As single agents, they decrease total cholesterol and low-density lipoprotein (LDL) cholesterol while increasing HDL cholesterol, in contrast to the metabolic effects of beta-blocking agents. Their mode of action is to promote vascular relaxation by blocking postganglionic nor-epinephrine vasoconstriction in the peripheral vascular smooth muscle. *Prazosin* and *doxazosin* are two preparations available in this class. A serious side effect of these drugs, which is most commonly described in the elderly patients, is called the "first-dose effect." In susceptible individuals, severe orthostasis has been reported when therapy was initiated and subsided after several days. When alpha₁-adrenergic drugs are used in combination with diuretics, hypotension may be further exacerbated. Therapy should begin with small doses taken at bedtime followed by incremental increases. Other side effects that may limit the usefulness of these agents in some patients include tachycardia, weakness, dizziness, and mild fluid retention.

Angiotensin-Converting Enzyme Inhibitors

The angiotensin-converting enzyme (ACE) inhibitors have rapidly become first-line drugs in the treatment of hypertension. Their rapid rise in popularity is due to the introduction of new formulations, which allow dosing once or twice a day with a good therapeutic response. There are relatively few side effects; chronic cough is the most worrisome and is a common reason of discontinuing the use of this group of drugs. Other side effects are occasional first-dose hypotension and blood dyscrasias. Occasionally, patients will suffer from rashes, loss of taste, fatigue, or headaches. Other agents should be considered for patients at risk for pregnancy (a strict contraindication). ACE inhibitors can be used in combination with other agents, including diuretics, calcium channel antagonists, and beta-blocking agents. In contrast to beta-blocking agents, these medications can be used in patients with asthma, depression, and peripheral vascular disease. For unknown reasons, they are less effective in African Americans unless a diuretic is used concomitantly. Use with diuretics increases the effectiveness of both drugs, but hypovolemia may result. If renal failure is present, hyperkalemia may result from potassium supplementation and altered tubular metabolism.

Any NSAID, including aspirin, may decrease the antihypertensive effectiveness. Use of NSAIDs, volume depletion, and renal artery stenosis may precipitate acute renal failure when administration an ACE inhibitor is initiated. Therefore, **creatinine levels should be measured at the start of therapy and 1 week after initiation**

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of any ACE inhibitor. An increase of up to 35% of the baseline creatinine value is acceptable, and treatment should be continued unless hyperkalemia develops.

Angiotensin-receptor Blockers

The angiotensin-receptor blockers such as *losartan* and *valsartan* interfere with the binding of angiotensin II to AT1 receptors. As with ACE inhibitors, they are effective in lowering blood pressure without causing the side effect of coughing. Angiotensin-receptor blockers also have favorable effects on the progression of kidney disease in individuals who have diabetes, as well as on those without diabetes and heart failure.

Calcium-channel Blockers

Calcium-channel blockers represent a major therapeutic breakthrough for patients with coronary artery disease. They have been found to be effective in patients with hypertension and peripheral vascular disease. The mechanism of action is to block calcium movement across smooth muscle, therefore promoting vessel wall relaxation. Calcium channel blockers are useful in treating concurrent hypertension and ischemic heart disease as an alternative to beta-blockers, if needed. Additionally, these drugs have been shown to be particularly effective in the elderly and African Americans. Side effects noted include headache, dizziness, constipation, gastroesophageal reflux, and peripheral edema. The addition of long-acting calcium-channel blockers has made these preparations more amenable for use in hypertension. A relative contraindication for use of these drugs is the presence of heart failure or conduction disturbances.

Direct Vasodilators

Hydralazine is a potent vasodilator used for years in obstetrics for severe hypertension associated with preeclampsia/eclampsia. The mechanism of action is direct relaxation of vascular smooth muscle, primarily arterial. Major side effects include headaches, tachycardia, and fluid (sodium) retention that may result in paradoxical hypertension. Several combinations have been used to counter the side effects and enhance antihypertensive effects. Diuretics may be added to reverse fluid retention caused by excess sodium. When used in combination with beta-blockers, tachycardia and headaches may be controlled without compromising the objective of lowering blood pressure. Drug-induced lupus has been widely stated as a potential side effect but is rare with normal therapeutic doses of 25 to 50 mg three times daily. *Minoxidil* is another extremely potent drug in this class, but is of limited use to the gynecologist because of its side effects in women (beard growth). Because of *minoxidil's* potency, only experienced practitioners should use it.

Central-acting Agents

Central-acting agents (*methyldopa* and *clonidine*) have long been used in obstetrics. The mechanism of action is to inhibit the sympathetics in the central nervous system, resulting in peripheral vascular relaxation. Side effects, including taste disorders, dry mouth, drowsiness, and the need for frequent dosing (except for the transdermal form of *clonidine*), have limited the popularity of this group of drugs. **Sudden withdrawal of *clonidine* may precipitate**

a hypertensive crisis and induce angina. The *clonidine* withdrawal syndrome is more likely to occur with concomitant use of beta-blockers. Compliance is always a major issue, and side-effect profiles contribute significantly to patient nonadherence. With the introduction of new classes of drugs with improved efficacy and reduced side effects, use of medications in this class is expected to decline.

Monitoring Therapy

Blood pressure readings should be monitored frequently by a nurse, the patient, or in the office at 1- to 2-week intervals. If the patient has other diseases (i.e., cardiovascular,

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renal), therapy should be initiated earlier and directed to the target organ. If lifestyle modification alone is successful, close monitoring is necessary at 3- to 6-month intervals. When lifestyle modification is unsuccessful, a blood pressure medication should be started to decrease target organ disease.

When beginning therapy, concurrent medical conditions treatable with a common agent should be sought. Sex is not an important consideration in choosing an antihypertensive agent.

Concurrent diseases or race are important for patients who:

- **Have migraine headaches, for which beta-blockers or calcium channel agonists may be the best choice**
- **Are African American and are likely to respond better to a combination of diuretics and calcium channel blockers**
- **Have diabetes, chronic kidney disease, and heart failure, for which ACE inhibitors should be used**
- **Have had myocardial infarctions and should receive beta-blockers because they reduce the risk for sudden death and recurrent myocardial infarctions.**

A summary of the compelling indications for individual drug classes is listed in Table 9.7.

Once antihypertensive medications are initiated, monitoring should be instituted at approximately monthly intervals to determine blood pressures and to assess side effects. Patients with stage 2 hypertension or with complicated comorbid illnesses may need more frequent monitoring. The serum creatinine and potassium levels should be monitored 1 to 2 times per year. When blood pressure goals are reached, patients may be seen in the office at 3- to 6-month intervals. Selected agents and dosages for therapy are listed in Table 9.8 and are not meant to be all inclusive. Patients capable of home blood pressure monitoring should be encouraged to measure blood pressure at the same time twice weekly (32). A log should be maintained for physician review of effectiveness of therapy.

If intolerable side effects develop, a different class of medications should be used and the patient's progress monitored. Patients whose blood pressure is difficult to control with two agents should be considered for referral. Causes of resistance to therapy include diseases missed during the initial evaluation, unrecognized early end-stage disease, and poor compliance. Patients with evidence of target organ disease should also be considered for referral to the appropriate specialist for more intensive diagnostic workup and therapy.

Cholesterol

The observation "*cholesterol is the most highly decorated small molecule in biology*" is testimony to the complexity of its role in cardiovascular disease (33). The dietary influence of cholesterol on atherosclerosis and its relationship to hypertension and cardiovascular events (myocardial infarction and stroke) has been widely debated in both the scientific and lay communities (34). The controversy centers on the effect of dietary cholesterol in assessing risk and prevention of cardiovascular disease (35). Many assume that all cholesterol and fat in the diet have negative health consequences. Furthermore, cholesterol metabolism is complex, and our understanding in some cases is extrapolated from animal models. The role of cholesterol testing (who, when, and at what age) is hotly debated among health care professionals, and the test itself is fraught with multiple variables that affect results. Understanding the metabolism of cholesterol will help identify and treat patients at risk of complications from hypercholesterolemia.

Terms and Definitions

Cholesterol is usually found in an esterized form with various proteins and glycerides that characterize the stage of metabolism. The following components are important lipid particles in cholesterol metabolism.

Table 9.8 Selected Medications and Dosage for Control of Essential Hypertension

Medication Class	Normal Daily Dosage (mg/day)	Daily Frequency
ACE inhibitors		
<i>Enalapril (Vasotec)</i>	2.5–40	1–2
<i>Captopril (Capoten)</i>	25–100	2
<i>Benazepril (Lotensin)</i>	10–40	1–2
<i>Fosinopril (Monopril)</i>	10–40	1
<i>Lisinopril (Prinivil, Zestril)</i>	10–40	1
<i>Moexipril (Univasc)</i>	7.5–30	1
Calcium channel blockers nondihydropyridines		
<i>Verapamil, sustained release (Calan SR, Isoptin SR)</i>	120–360	1–2
<i>Diltiazem, sustained release (Cardizem CD, Tiazac)</i>	180–420	1
Calcium channel blockers dihydropyridines		
<i>Amlodipine (Norvasc)</i>	2.5–10	1
<i>Felodipine (Plendil)</i>	2.5–20	1
<i>Nifedipine, long-acting (Adalat CC, Procardia XL)</i>	30–60	1
<i>Nicardipine, sustained release (Cardene SR)</i>	60–120	2
α-blockers		
<i>Terazosin (Hytrin)</i>	1–20	1–2
<i>Doxazosin (Cardura)</i>	1–16	1
Mixed α- and β-blockers		
<i>Labetalol (Normodyne, Trandate)</i>	200–800	2
Thiazide diuretics		
<i>Hydrochlorothiazide (Microzide, HydroDIURIL)</i>	12.5–50	1
<i>Indapamide (Lozol)</i>	1.25–2.5	1

Loop diuretics		
<i>Furosemide (Lasix)</i>	20–80	2
<i>Bumetanide (Bumex)</i>	0.5–2	2
Potassium-sparing diuretics		
<i>Triamterene (Dyrenium)</i>	50–100	1–2
β-blockers		
<i>Atenolol (Tenormin)</i>	25–100	1
<i>Metoprolol (Lopressor)</i>	50–100	1–2
<i>Metoprolol, extended release (Toprol XL)</i>	50–100	1
Angiotensin II receptor antagonists		
<i>Losartan (Cozaar)</i>	25–100	1–2
<i>Valsartan (Diovan)</i>	80–320	1
<i>Candesartan (Atacand)</i>	8–32	1
Central α_2-agonist		
<i>Clonidine (Catapres)</i>	0.1–0.8	2
<i>Clonidine patch (Catapres TTS)</i>	0.1–0.3	weekly
Direct vasodilators		
<i>Hydralazine (Apresoline)</i>	25–100	2
<i>Minoxidil (Loniten)</i>	2.5–80	1–2

ACE, angiotensin-converting enzyme.

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Chylomicrons This large lipoprotein particle consists of dietary triglycerides and cholesterol. Chylomicrons are secreted in the intestinal lumen, absorbed in the lymph, and then passed into general circulation. In adipose tissue and skeletal muscle, they adhere to binding sites on the capillary wall and are metabolized for energy production.

Lipoprotein Particle A lipoprotein particle is made from three major components. The core consists of nonpolar lipids (triglycerides and cholesterol esters), which are present in varying amounts depending on the stage of the metabolic pathway in which they are found. Surrounding the nonpolar core is a surface coat of phospholipids, which are made of apoproteins and structural proteins.

Apoprotein Attached to all lipoprotein particles is an apoprotein. This is a specific recognition protein exposed at the surface of a lipoprotein particle. Apoproteins have specific receptors and demarcate the stage of cholesterol metabolism. Certain apoproteins are associated with specific types of cholesterol. For example, apoprotein A-I and apoprotein A-II are associated with HDL cholesterol, the so-called scavenger cholesterol. Apoprotein CII has additional activity as a cofactor for lipoprotein lipase.

Lipoprotein Classes Lipoprotein particles are separated into five classes based on physical characteristics. Lipoprotein classes are determined by the separation of lipids in an electrophoretic field; however, *in vivo* they are in a continuum. The various cholesterol metabolites are separated by density. As lipoprotein particles are metabolized and lipids are removed for energy production, they become more dense. Additionally, attached apoproteins are modified as cholesterol moves from the so-called exogenous pathway (dietary) to the endogenous pathway (postabsorption and metabolized by the liver).

Following are the subdivisions of the lipoprotein classes (Fig. 9.3).

Prehepatic Metabolites

Chylomicrons and remnants are composed of major lipids and apoproteins of the A, B-48, C, and E classes. Their density is 1.006 g/mL. As expected, these are large particles made up of dietary cholesterol molecules that are absorbed with triglycerides.

Posthepatic Metabolites

Very low-density lipoproteins (VLDL) are transient remnants found after initial liver metabolism and compose only 10% to 15% of cholesterol particles. They consist of

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endogenously synthesized triglycerides with a density of 1.006 g/mL. The diameter is considerably smaller than the chylomicrons, ranging from 300 to 800 nm.

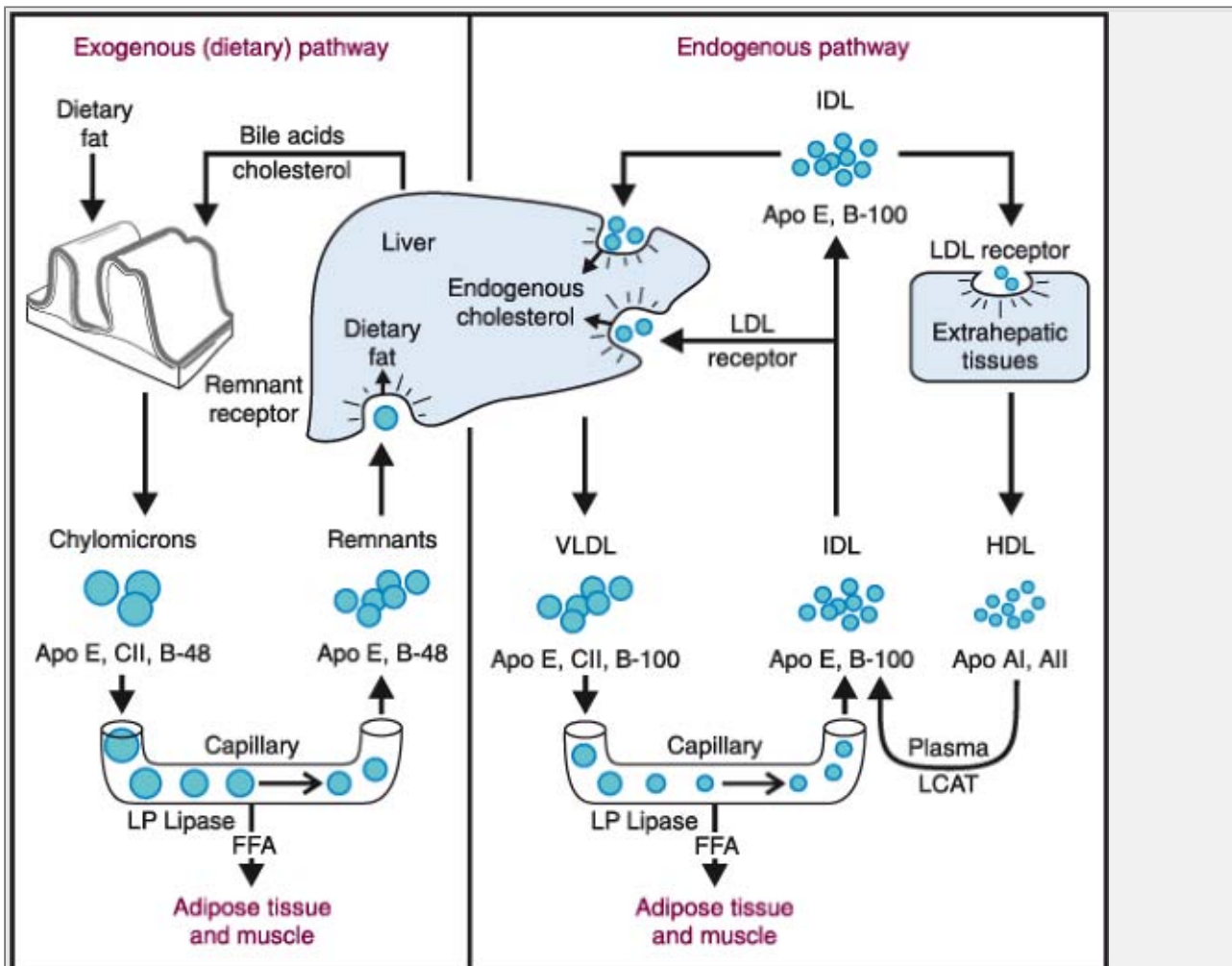


Figure 9.3 Metabolic pathways of lipid metabolism. Apo, apoprotein; LP, lipoprotein; FFA, free fatty acid; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; LCAT, lecithin cholesterol acyltransferase.

Intermediate density lipoproteins (IDL) consist of cholesterol esters, which are posthepatic remnants derived from dietary sources. Associated apoproteins are B-100, CIII, and E. Apoprotein B-48 is lost after the initial hepatic metabolism, and B-100 is substituted. Apoprotein E, which is a liver recognition apoprotein, is found only in VLDL and IDL. Metabolites of IDL are transient lipoproteins measured only in certain pathologic conditions.

The density is 1.019 g/mL with a diameter of 250 nm—a significant drop in diameter from 800 nm found in the VLDL.

Low-density lipoprotein (LDL) is mainly composed of the cholesterol ester and is associated with B-100 apoprotein. LDL cholesterol is approximately 60% to 70% of total cholesterol. Elevated levels of LDL cholesterol have been associated with increased myocardial infarction in women older than 65 years of age. There is structural class called LDL (a') that is associated with myocardial infarction. A family history of structurally abnormal B-100 apoprotein indicates a high risk for myocardial infarction resulting from lipid buildup and premature atherosclerosis (36). Density ranges from 1.019 to 1.063, with a diameter of 180 to 280 nm.

High-density lipoprotein (HDL) is composed of cholesterol esters with apoproteins A-I and A-II. These particles are 20% to 30% of total cholesterol and are the most dense with a weight of 1.063 to 1.120 g/mL. The diameter of this group of proteins is 50 to 120 nm.

Metabolism

Cholesterol metabolism is divided into two pathways: (i) the exogenous pathway derived from dietary sources, and (ii) the endogenous pathway or the lipid transport pathway. Individuals vary in their ability to metabolize cholesterol, with patients classified as normals, hyporesponders, and hyperresponders (37). Hyporesponders may be given cholesterol-loaded diets with no effect on serum cholesterol measurements. Hyperresponders, in contrast, have high serum cholesterol levels, regardless of dietary intake. Explanations for these differences are well described in animal models, but not in humans.

Once a meal is eaten, cholesterol is transported as dietary fat. The average daily American diet contains approximately 100 g of triglyceride and approximately 1 g of cholesterol daily. Dietary fats are saponified in the intestinal lumen by pancreatic lipases and synthesized into chylomicrons, which are first absorbed by active transport into intestinal lymph and then into the general circulation. Capillaries in the adipose tissue and skeletal muscle are able to incorporate triglycerides and fats by the action of lipoprotein lipase, as depicted in Figure 9.3. Metabolic utilization may occur during either phase of metabolism (dietary or endogenous). During absorption and synthesis of chylomicrons, apoproteins are incorporated. Apoprotein C-II is important as a cofactor to activate lipoprotein lipase, which enzymatically liberates fatty acids (for energy) and monoglycerides. These fatty acids may enter endothelial, adipose, or muscle cells, where they are either oxidized into active metabolic products or re-esterified to triglycerides.

Triglycerides are found in the core lipoprotein particles and are removed through the capillary endothelium and the chylomicron. Predominant apoproteins are B-48 or B-100 and E apoproteins. When chylomicron synthesis occurs in the intestine, the primary B apoprotein is B-48; upon leaving adipose cells, muscle cells, or the liver, the second B apoprotein or B-100 is substituted. Abnormal forms of B-100 are associated with premature cardiovascular disease and are currently used as genetic markers in research laboratories (38). Another apoprotein added during cellular metabolism is apoprotein E. Apoprotein E is important in liver recognition of chylomicron remnants. Theories suggest that hypo- and hyperresponses to dietary cholesterol may occur secondary to the liver's ability to recognize and metabolize apoprotein E (39). In the animal model, populations with large numbers of liver receptors for apoprotein E easily metabolize cholesterol and are labeled hyporesponders. Individuals with a reduced number of apoprotein E receptors are unable to metabolize cholesterol as readily, which increases the number of lipid particles. These individuals are considered hyperresponders. Despite dietary cholesterol modification,

these individuals continue to have high serum cholesterol levels.

After metabolic degradation of dietary chylomicrons, apoprotein substitution occurs and liver metabolism of cholesterol esters begins. Lipid transport is now in the *endogenous pathway*. Carbohydrates are synthesized to fatty acids and esterified with glycerol to form triglycerides. These newly formed triglycerides are not of dietary origin and are placed in the core of VLDL. These particles are relatively large and carry five to ten times more triglyceride than cholesterol esters with apoprotein B-100. Hypertriglyceridemia is an independent risk factor for cardiovascular disease (40). The relationship between hypertriglyceridemia and cardiovascular disease is well known but poorly defined.

VLDL particles are transported to tissue capillaries, where they are broken down to usable fuels, monoglycerides, and fatty acids. Apoproteins C and E are still present within this lipoprotein particle. After metabolic enzymatic degradation in the peripheral tissues, IDL remains and is either catabolized in the liver by binding to LDL receptors or modified in the peripheral tissues. As noted previously, they are associated with apoprotein E receptors, the liver recognition receptors. During the transformation from IDL to LDL cholesterol, all apoproteins are removed, except apoprotein B-100. The LDL cholesterol, or the so-called high-risk cholesterol, is found in high circulating levels.

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Despite the negative connotation of LDL in cardiovascular disease, it is a very important cellular metabolite and precursor for adrenocortical cells, lymphocytes, and renal cells. LDL receptors on cell surfaces allow for incorporation of LDL into cellular metabolism. In target cells, these lipid particles are hydrolyzed to form cholesterol for use in membrane synthesis and as precursors for steroid hormones (such as estrogen and progesterone). Once the cell has incorporated the necessary cholesterol, the cell surface receptor reforms, limiting further absorption. The liver uses LDL for synthesis of bile acids and free cholesterol, which is secreted into the bile. In the normal human, 70% to 80% of LDL is removed from the plasma each day and secreted in the bile by utilization of the LDL receptor pathway.

The final metabolic pathway is the transformation of HDL cholesterol in extrahepatic tissue. HDL cholesterol carries the plasma enzyme lecithin cholesterol acyltransferase (LCAT). LCAT allows HDL cholesterol to resynthesize lipids to VLDL cholesterol and recycle the lipid cascade. The fate of newly synthesized VLDL cholesterol is the same as absorbed VLDL, and it eventually becomes LDL cholesterol. HDL cholesterol acts as a "scavenger" and therefore reverses the deposit of cholesterol into tissues. There is good evidence that HDL cholesterol is responsible for the reversal of atherosclerotic changes in vessels, hence the term *good cholesterol* (41,42).

Hyperlipoproteinemia

When cholesterol is measured, various fractions are reported. Plasma cholesterol or total cholesterol consists of cholesterol and unesterified cholesterol fractions. If triglycerides are analyzed in conjunction with cholesterol, then assumptions can be made concerning which metabolic pathway may be abnormal. Elevation of both total cholesterol and triglycerides signifies a problem with chylomicrons and VLDL synthesis. If the triglyceride-to-cholesterol ratio is greater than 5:1, the predominant fractions are chylomicrons and VLDL. A triglycerides-to-cholesterol ratio less than 5:1 signifies a problem in the VLDL and LDL fractions.

Hyperlipoproteinemias are defined by establishing a "normal population" and then setting various limits at the 10th and 90th percentiles. Recent standards for women set the 80th percentile for cholesterol at 240 mg/dL and the 50th percentile at 200 mg/dL (Table 9.9). Researchers continue to debate different cutoff limits depending on the amount

of fat versus vegetable and fiber consumption within the diet of specific populations (43).

Plasma elevations of chylomicrons, LDL, VLDL, various remnants of IDL, and VLDL are classified by the elevated fraction. This adds to the confusion of an already complex topic. Unfortunately, this classification of hyperlipoproteinemias is the basis of studying of disease states.

Evaluation

The consensus of most researchers is that office laboratory analysis of total cholesterol is virtually worthless as an accurate measure of cholesterol levels. The measurement techniques and standardization of machines are difficult to maintain, and there is a wide variation in readings (44). Therefore, despite their popularity, these techniques are totally inadequate for either screening or monitoring the treatment of patients with hypercholesterolemia.

There are multiple environmental causes of variation in cholesterol measurements (45). **Major sources of variation within individuals include diet, obesity, smoking, ethanol intake, and the effects of exercise.** Other clinical conditions that affect cholesterol measurements include hypothyroidism, diabetes, acute or recent myocardial infarction, and recent weight changes. Measurements also can be altered by fasting, position of the patient

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while the sample is drawn, the use and duration of venous occlusion, various anticoagulants, and the storage and shipping conditions (46).

Table 9.9 Initial Classification Based on the Total Cholesterol, LDL, HDL, and Triglyceride Levels

Initial Classification	
Total cholesterol	
<200 mg/dL	Desirable blood cholesterol
200–239 mg/dL	Borderline high blood cholesterol
≥240 mg/dL	High blood cholesterol
LDL cholesterol	
<100 mg/dL	Optimal cholesterol
100–129 mg/dL	Near or above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
HDL cholesterol	
<40 mg/dL	Low HDL cholesterol
≥60 mg/dL	High HDL cholesterol
Triglycerides	
<150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
>500 mg/dL	Very high

LDL, low-density lipoprotein; HDL, high density lipoprotein.

Adapted from the **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults**. *JAMA* 2001;285:2486–2497.

Factors Affecting Test Results

Intrapersonal variation has been well described. If a single individual has total cholesterol measured four times during the day, the variation is 2.5%. If retested within 1 month, on a twice-weekly basis, the coefficient of variation increases to 4.8%. Monthly measurements over 1 year may result in a variation as high as 6.1%. Therefore, **at least two and preferably four specimens should be taken 1 month apart should be collected in the same dietary state in order for a lipid value to be considered accurate.**

Age and sex contribute to variations in total cholesterol measurements. Before age 50, women have lower lipid values than men, after which age the level in women is higher than in men. This finding may be modified by exogenous oral conjugated estrogens. The genetic basis for interpersonal variability is thought to be a mediated by apolipoprotein receptors.

Seasonal variation also occurs. In December or January, lipid samples have been found to be approximately 2.5% higher than those measured in June or July. LDL and total cholesterol levels were higher, whereas there was no significant variation found for HDL. The

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index population was found to weigh approximately 6% more in December and January than in June or July, which may account for the differences.

The effect of diet and obesity has been well established. Some researchers felt this effect may be related to hypo- and hyperresponder status. However, weight reduction in an obese individual generally affects the triglyceride level, which may decrease as much as 40%. Total cholesterol and LDL decrease less than 10% with diet; however, HDL increases approximately 10%. Weight gain negates any benefit from prior weight loss. Therefore, accuracy of lipid measurements depends on the stability of the patient's weight.

Alcohol and cigarette smoking are well-known modifiers of cholesterol.

Moderate sustained alcohol intake increases HDL and decreases LDL; however, there is a complimentary increase in triglycerides. Alcohol has a protective effect when taken in moderation (defined as approximately 2 ounces of absolute alcohol/day), but this effect is negated in higher quantities. The increase in HDL is in the HDL₁₃ fraction, which is important in the scavenger mechanism of removing LDL. Smoking has the opposite effect, increasing LDL and triglyceride levels and decreasing HDL. HDL₃ decreases with cigarette smoking. The critical number of cigarettes smoked is 15 to 20 per day, regardless of sex, and a variation in the number smoked will affect results. Caffeine has a mixed effect on lipoprotein measurements but should be avoided in the 12 hours before blood collection.

Exercise is an important variable in the overall risk management of heart disease. Moderate levels of exercise are as important in overall cardiovascular health as control of hypertension and cessation of cigarette smoking. Strenuous exercise lowers the concentrations of triglycerides and LDL and increases HDL in the serum. Because of these acute blood changes, vigorous exercise should be avoided within 12 hours of drawing of the blood for testing.

Certain disease states and medications affect cholesterol measurements. Use of diuretics and *propranolol* increases triglycerides and decreases HDL. Diuretics may also

increase total cholesterol levels. Diabetes, especially in the presence of poor control, may be associated with very high levels of triglycerides and LDL and decreased levels of HDL. This may explain why these individuals are prone to cardiovascular diseases. Patients with diabetes under tight control generally have improved lipoprotein profiles.

Pregnancy is associated with decreased total cholesterol in the first trimester and continuous increases of all fractions over the second and third trimesters (47). The LDL and triglyceride concentrations are the lipoproteins most affected by pregnancy. Limited studies have been done on standardization of lipid levels in pregnancy. Because of the short span, interventions are of little clinical significance.

Patients with hypothyroidism also have increased levels of total cholesterol and LDL.

Testing

Because the diurnal variation of blood triglycerides, blood samples should be collected in the morning after a 12-hour fast. Excessive quantities of water should not be consumed before blood is drawn. The patient should be sitting quietly for approximately 15 minutes before blood drawing. Patients who were placed in the supine position for 30 minutes and then required to stand for 30 minutes had a 9% increase in total cholesterol, LDL, and VLDL fractions, while HDL increased by 10% and triglycerides increased by 12%. Additionally, if the tourniquet is in place more than 5 minutes, causing vascular stasis, all measurements increase by 10% to 15%. After even 2 minutes of venous occlusion, serum cholesterol levels can increase 2% to 5%. Therefore, the sample used for cholesterol testing should be collected first if multiple blood samples are required. Finger

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sticks are approximately 8.5% lower for all component measurements than venous blood as a result of contamination from interstitial and lymph fluids.

Collection tube anticoagulants may have a profound effect on lipoproteins. The total cholesterol has been observed to change depending on the anticoagulant used: EDTA increases measurements by 3%, oxalate increases by 9%, citrate increases by 14%, and fluoride by 18%. EDTA is considered the standard anticoagulant for cholesterol measurement. If cholesterol measurements cannot be analyzed within a reasonable time, the samples may be stored at 0°C for up to 4 days, at -20°C for 6 months, or at -50° to -80° indefinitely. Specimens transported by mail should be placed on dry ice.

One of the most important aspects of overall standardization of lipoprotein measurements is the laboratory used. Currently, laboratory levels should be within $\pm 5\%$ of the Centers for Disease Control and Prevention standards for lipoprotein measurements. Approximately 80% of labs in one study met these criteria (48). Therefore, to accurately assess cholesterol values, the clinician should be knowledgeable about the laboratory used. It may be worthwhile to consult a clinical pathologist to determine if the laboratory complies with CDC standards for cholesterol and lipoprotein measurements.

Management

Once hyperlipidemia is confirmed on at least two separate occasions, secondary causes should be diagnosed or excluded by taking a detailed medical and drug history, measuring serum creatinine and fasting glucose levels, and testing thyroid and liver function. Causes of secondary dyslipidemia include diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and use of medications such as progestins, anabolic steroids, and corticosteroids. **Therapeutic lifestyle changes should be initiated in all patients to reduce their risk of coronary heart disease:**

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg/d)
- **Therapeutic options for enhancing LDL lowering, such as plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10–25 g/d)**
- **Weight reduction**
- **Increased physical activity**

Figure 9.4 is a suggested algorithm for cholesterol control based on LDL levels. Cholesterol fat-lowering diet books abound in most bookstores and allow the patient to choose a diet she will best follow. **The role of exercise and cigarette cessation should be stressed to all patients. Patients with a family history of cardiovascular disease (history of premature coronary artery problems and strokes) should be tested and started on conservative programs in their 20s.** After 3 to 6 months, if the LDL remains above 160 mg/dL with zero to one risk factor or above 130 mg/dL with two or more risk factors, then medical therapy should be initiated. Any woman with coronary heart disease or equivalents such as diabetes or other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease) should initiate lifestyle changes if her LDL is ≥ 100 mg/dL and drug therapy if her LDL is ≥ 130 mg/dL. Anyone with an LDL ≥ 190 mg/dL should be considered for drug therapy (49).

The bile acid-binding resins *cholestyramine* and *colestipol* were long the mainstay of therapy. Their usefulness is limited by side effects such as constipation, bloating, nausea, and heartburn, as well as by their tendency to interfere with the absorption of other drugs. *Nicotinic acid* 500 mg three times daily decreases triglycerides, LDL, and

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lipoprotein(a) and increases HDL more than any other drug. However, flushing, pruritus, gastrointestinal distress, and, rarely, hepatotoxicity are a few of the adverse effects of *nicotinic acid*. Starting at a low dose and pretreating with *aspirin* 325 mg or *ibuprofen* 200 mg can minimize the facial flushing. Fibric acid derivatives like *clofibrate* and *gemfibrozil* are used mainly to lower triglycerides and increase HDL but may increase LDL in some patients. The HMG-CoA reductase inhibitors (statins) include *atorvastatin*, *fluvastatin*, *lovastatin*, *pravastatin*, and *simvastatin*. These medicines inhibit HMG-CoA (3-hydroxy-3methyl-glutaryl-coenzyme A) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis.

Several clinical trials have shown that *pravastatin*, *simvastatin*, and *lovastatin* have a beneficial effect in cardiovascular disease. Statins are generally better tolerated than other lipid-lowering drugs, but reported effects include severe myalgias, muscle weakness with increases in creatine phosphokinase, and, rarely, rhabdomyolysis leading to renal failure. Symptomatic hepatitis is rare, but serum glutamic oxaloacetic transaminases should be measured at baseline, at 6 and 12 weeks after initiation of therapy, and semiannually once therapeutic levels are reached. *Atorvastatin*, *lovastatin*, and *simvastatin* are metabolized by the CYP3A4 enzyme system (50). Medications that inhibit this enzyme include the azoles antifungals, *erythromycin*, *clarithromycin* (*Biaxin*), *verapamil* (*Calan*), *diltiazem* (*Cardizem*), *nefazodone* (*Serzone*), *fluvoxamine* (*Luvox*), and *cyclosporine*. Grapefruit juice can also inhibit the action of CYP3A4. When these medications are used with the aforementioned statins, their levels can be increased, which increases the risk of myopathy and rhabdomyolysis. All the statins except *pravastatin* can increase the effect of warfarin and lead to an increase in

the coagulation time as reflected by an increase in international normalized ratio (INR). Thus,

patients taking these drugs in combination should be closely monitored. The commonly used statins are listed in Table 9.10.

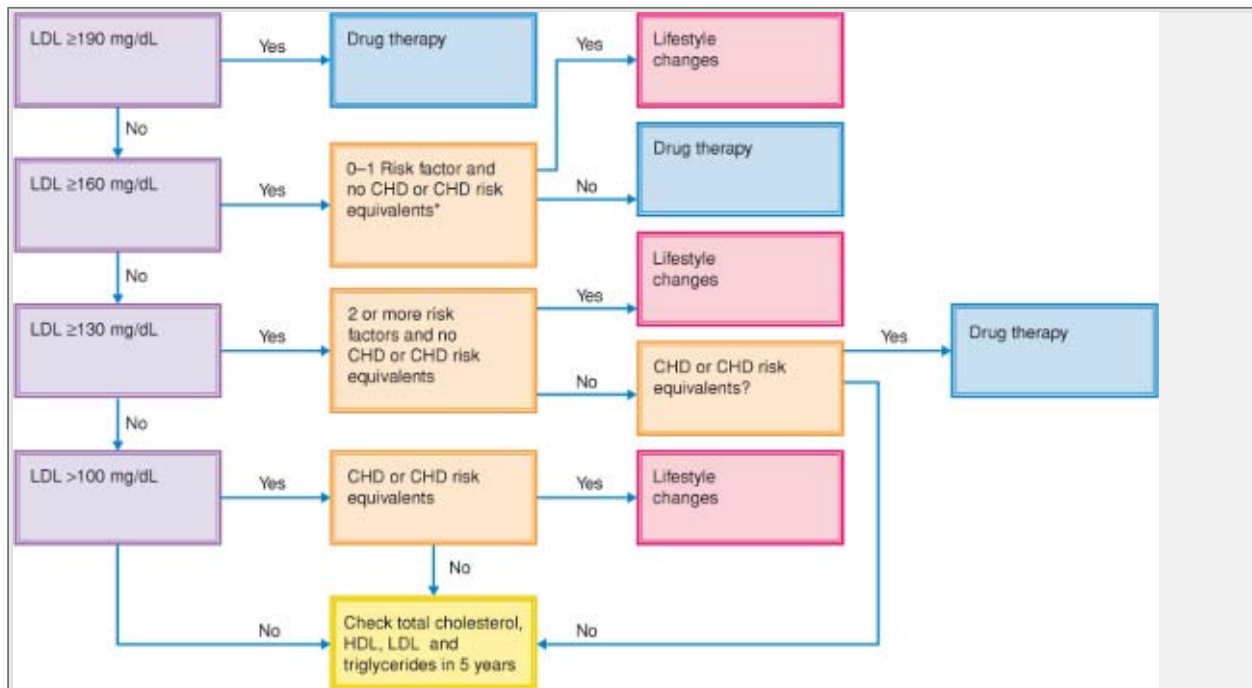


Figure 9.4 Treatment decisions based on the LDL cholesterol. LDL, low-density lipoprotein; HDL, high-density lipoprotein. * Coronary Heart Disease (CHD) risk equivalents: Diabetes or other forms of atherosclerotic disease like peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease. (Adapted from the **Third Report of the National Cholesterol Education Program [NCEP] Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults**. *JAMA* 2001;285:2486–2497.)

Table 9.10 Commonly Used Statin Agents

<i>Generic</i>	<i>Trade Name</i>	<i>Daily Dose</i>	<i>Renal Function</i>
Lovastatin	<i>Mevacor</i>	20 mg, 40 mg, 80 mg daily	Use lower dose for severe renal impairment
Pravastatin	<i>Pravachol</i>	10 mg, 20 mg, 40 mg, 80 mg daily	Use lower dose for severe or moderate renal impairment
Simvastatin	<i>Zocor</i>	10 mg, 20 mg, 40 mg, 80 mg daily	Use lower dose for severe renal impairment
Fluvastatin	<i>Lescol</i>	20 mg, 40 mg, 80 mg daily	No dose adjustment needed for reduced renal function
Atorvastatin	<i>Lipitor</i>	10 mg, 20 mg, 40 mg, 80 mg daily	No dose adjustment needed for reduced renal function

Diabetes Mellitus

Diabetes mellitus is a chronic disorder of altered carbohydrate, protein, and fat metabolism resulting from a deficiency in the secretion or function of insulin. The disease is defined by the presence of either fasting hyperglycemia or elevated plasma glucose levels based on an

oral glucose tolerance testing (OGTT). The major complications of DM are primarily vascular and metabolic. The prevalence of DM is higher in women and certain ethnic groups, although a background rate in the general population is 2.5% (51). **Risk factors for DM are:**

- **Age greater than 45 years**
- **Adiposity or obesity**
- **A family history of diabetes**
- **Race/ethnicity**
- **Hypertension (140/90 or greater)**
- **HDL cholesterol less than or equal to 35 mg/dL and/or a triglyceride level greater than or equal to 250 mg/dL**
- **History of gestational diabetes or delivery of baby more than 9 pounds**

Major complications of DM include blindness, renal disease, gangrene of an extremity, heart disease, and stroke. Diabetes is one of the four major risk factors for cardiovascular disease (52).

Classification

In January 1999, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus published a report revising the system that had been in use since 1979 (53,54). The goal of the revision is to provide guidelines for nomenclature and testing that may reduce diagnostic confusion and improve patient well-being (Table 9.11). The terms

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insulin dependent diabetes mellitus (IDDM) and *noninsulin dependent diabetes mellitus* (NIDDM) should no longer be used and have been replaced by the terms type 1 and type 2 diabetes mellitus.

Table 9.11 Classification of Diabetes Mellitus

1. Type 1 diabetes
Characterized by pancreatic destruction leading to insulin deficiency
A. Idiopathic
B. Immune mediated
2. Type 2 diabetes
A combination of insulin resistance and some degree of inadequate insulin secretion
3. Other types of diabetes:
A. Impaired glucose tolerance (IGT)
B. Endocrinopathies (Cushing's, acromegaly, pheochromocytoma, hyperaldosteronism)
C. Drug- or chemical-induced
D. Diseases of the exocrine pancreas (pancreatitis, neoplasia)

E. Infections
F. Genetic defects of beta-cell function and insulin action
G. Gestational diabetes mellitus

Adapted from **The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.** *Diabetes Care* 2000; 23: S4–S42.

Type 1 Diabetes Mellitus

With type 1 diabetes, the major metabolic disturbance is the absence of insulin from destruction of beta cells in the pancreas. Insulin is necessary for glucose metabolism and cellular respiration. When insulin is absent, ketosis results. The cause of type 1 diabetes is unknown; however, data suggest an autoimmune association from either a viral infection or toxic components in the environment. Studies in the past decade have shown a correlation between many autoimmune diseases and the human leukocyte antigens (HLA).

Insulin-sensitive tissues (muscle, liver, and fat) fail to metabolize glucose efficiently in the absence of insulin. In uncontrolled type 1 diabetes, an excess of counterregulatory hormones (cortisol, catecholamines, and glucagon) contributes to further metabolic dysfunction. In the absence of adequate amounts of insulin, increasing breakdown products of muscle (amino acid proteolysis), fat (fatty acid lipolysis), and glycogen (glucose glycogenolysis) are recognized. Additionally, there is an increase in glucose production from noncarbohydrate precursors as a result of gluconeogenesis and ketogenesis in the liver. If not promptly treated, severe metabolic decompensation (i.e., diabetic ketoacidosis) will occur and may lead to death.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is a heterogeneous form of diabetes that commonly occurs in older age groups (>40 years) and is more frequently noted to have a familial tendency than type 1 diabetes. This form of diabetes mellitus accounts for approximately 90% to 95% of those with diabetes. The presence of risk factors strongly influences the development of type 2 diabetes in susceptible populations.

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Risk factors for type 2 diabetes include ethnicity, obesity, family history of DM, sedentary lifestyle, impaired glucose tolerance, upper-body adiposity, and a history of gestational diabetes and hyperinsulinemia.

In contrast to an absence of insulin that occurs with type 1 diabetes, in type 2 diabetes altered metabolism of insulin results in insulin resistance. This condition is characterized by impaired glucose uptake in target tissues. A compensatory increase in insulin secretion results, causing higher-than-normal circulating insulin levels (55). Obesity is present in 85% of affected patients. The cause of type 2 diabetes is unknown, but defects in both the secretion and action of insulin are suspected.

Many patients diagnosed with type 2 diabetes at an early age eventually exhaust endogenous pancreatic insulin and require injected insulin. When under severe stress, such as infection or surgery, they may develop diabetic ketoacidosis or a hyperglycemic hyperosmolar nonketotic state.

Diagnosis

Three methods are available to diagnose diabetes mellitus in nonpregnant women:

- **A single fasting blood glucose greater than or equal to 126 mg/dL on two separate occasions**
- **A random blood glucose equal to or above 200 mg/dL in an individual with classic signs and symptoms of diabetes (polydipsia, polyuria, polyphagia, and weight loss)**
- **A 2-hour OGTT greater than or equal to 200 mg/dL (fasting sample, 60-, and 120-minute samples) after a 75-g load of glucose. A 2-hour OGTT should not be performed if the first two criteria are present.**

Diagnostic criterion for impaired glucose intolerance (IGT) is a fasting glucose greater than or equal to 100 mg/dL but less than 126 mg/dL (54).

A 2-hour OGTT should be performed under the following conditions:

- A 10-hour fast should precede morning testing.
- The patient should sit throughout the procedure.
- No smoking is permitted during the test interval.
- Caffeinated beverages should not be consumed.
- More than 150 g of carbohydrates should be ingested for 3 days before the test.
- No drugs should be taken before the test.
- The patient should not be bedridden or under stress.

Patients who should be considered for diabetes testing are:

- **All individuals 45 years of age or older (repeat at 3-year intervals)**
- **Persons with classic signs and symptoms of diabetes (i.e., polyuria, polydipsia, polyphagia, and weight loss)**
- **Ethnic groups at high risk (Pacific Islanders, Native Americans, African Americans, Hispanic Americans, and Asian Americans)**
- **Obesity (body mass index >27 kg/m²)**

- **History of a first-degree relative with diabetes**
- **Women with gestational diabetes or have delivered a baby more than 9 pounds**
- **Individuals with hypertension (> 140/90)**
- **An HDL cholesterol level less than or equal to 35 mg/dL or triglyceride level greater than or equal to 250 mg/dL**
- **Presence of impaired glucose tolerance on previous testing**

Assessment of Glycemic Control

The only acceptable method for assessment of glycemic control is determination of blood glucose by direct enzyme analysis and not by measurement of urine values, which do not correlate. In the past decade, multiple adequate techniques using test strips and meters have been introduced. These machines work well but reflect whole blood determinations, not serum values. Upgrades of testing strips (in which blood does not need to be wiped away) and Glucometers with memory storage have made home glucose monitoring more reliable. Physician treatment guidelines are in Table 9.12 and patient guidelines in Table 9.13. A 10-multicenter study, the diabetes control and complication trial (DCCT) performed under the auspices of the National Institutes of Health, showed a marked reduction (40%–50%) in complications of neuropathy, retinopathy, and nephropathy when patients with type 1 diabetes received intensive therapy (accomplished by a team approach) as compared with those who received standard therapy.

Table 9.12 Physician Guidelines in the Therapy of Diabetes Mellitus

- Establish diagnosis and classify type of diabetes mellitus (DM).
- The oral glucose tolerance test (OGTT) is not recommended for routine clinical use because of its higher cost, time requirement, and limited reproducibility.
- Initiate diabetes education classes to learn blood glucose monitoring and diabetes medications; to learn signs, symptoms, and complications; and to learn how to manage sick days.
- Place patient on ADA diet with appropriate caloric, sodium, and lipid restrictions.
- Establish cardiac risk factors, kidney function (serum creatinine, urine for microalbuminuria).
- If neuropathy is present, refer to a neurologist.
- Establish extent of fundoscopic lesion (refer to ophthalmologist as needed).
- Check feet and toenails at least once a year and refer to a foot specialist.
- Use finger-stick blood glucose for daily diabetic control.
- Follow chronic glycemic control by HgA_{1c} every 2 to 3 months in the office.

- Initial general health evaluation should consist of a complete history and physical examination and the following laboratory tests: CBC with differential, chemistry profile, lipid profile, urinalysis, thyroid function tests, urine for microalbuminuria, and ECG (baseline at age 40 or older, repeat yearly).

- Oral hypoglycemic agents like the sulfonylureas may be considered if fasting blood glucose does not decline or increase and if the patient has diabetes for fewer than 10 years, does not have severe hepatic or renal disease, and is not pregnant or allergic to sulfa drugs.

- While on oral hypoglycemic agents, check the HgA_{1C} every 3 months and at least two times a year if stable.

- If the HgA_{1C} is <7% or the postprandial glucose is <200 mg/dL, omit the oral hypoglycemic agents, place on diet alone, and follow every 3 months.

- If the fasting serum glucose is >200 mg/dL consistently or the HgA_{1C} is more than 10%, consider starting insulin and referring the patient to an internist.

Administer the flu vaccine every fall and the pneumococcal vaccine every 6 years.

ADA, American Diabetic Association; HgA_{1C}, hemoglobin A_{1C}; CBC, complete blood count; ECG, electrocardiogram.

Adapted from **The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.** *Diabetes Care* 2000; 23: S4–S42.

Table 9.13 Patient Guidelines for Treatment of Type 2 Diabetes

- Initiate an ADA reducing diet (50% CHO, 30% fat, 20% protein, high fiber) with three meals a day.

- Maintain ideal body weight or to reduce weight by 5% to 15% in 3 months if obese.

- Modify risk factors (smoking, exercise, fat intake).

- Check fasting blood glucose by finger stick daily for 2 months. If FBS declines, no other therapy is needed. If FBG does not decline or increases, use of an oral hypoglycemic agent may be considered.

ADA, American Diabetic Association; CHO, carbohydrate; FBS, fasting blood glucose.

Adapted from **The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.** *Diabetes Care* 2000; 23: S4–S42.

Treatment

Type 2 diabetes is treated by a combination of lifestyle adjustments and medications.

Lifestyle

Diet is the most important component of DM management and usually the hardest way to achieve control. **Three major strategies are used: weight loss, low-fat diet (≤30% of calories from fat), and physical exercise.** Obese patients should reduce their weight to ideal body weight. Metabolic advantages of weight reduction are improved lipid profile and improved glucose control secondary to increased insulin sensitivity and decreased insulin

resistance. The greater the weight loss, the greater the improvement in lipid disorders. Physical exercise promotes weight loss and improves insulin sensitivity and dyslipidemia in those people who are in high-risk groups for cardiovascular and microvascular diseases (56).

Oral Hypoglycemic Agents

Oral hypoglycemic agents are recommended for many type 2 diabetic patients (57).

The first oral hypoglycemic agents introduced were first- and second-generation sulfonylureas. Other classes of drugs—such as biguanides, thiazolidinediones, alpha-glucosidase inhibitors, and *insulin* secretagogues—have been introduced that have different effects in patients with type 2 diabetes. Commonly used formulations of this class of drugs are listed in Table 9.14. The mode of action of sulfonylureas is based on two different mechanisms: (i) enhanced insulin secretion from the pancreas, and (ii) an extrapancreatic effect that is poorly understood. Endogenous insulin secretion (as measured by C-peptide) is necessary for OHA to work. Additionally, if the fasting blood glucose on an adequate diabetic diet is greater than 250 mg/dL, there is little effect. Frequent evaluation to monitor control (every 3–4 months) is important. If glucose levels cannot be controlled with oral hypoglycemic agents (i.e., sulfonylureas) or other medicines (i.e., *metformin*, a biguanide), insulin therapy should be initiated and referral should be considered because of the increased rate of complications.

Thyroid Diseases

Thyroid disorders are more common in women and some families although the exact rate of inheritance is unknown (58). In geriatric populations, the incidence may be as high as 5% (59). Unfortunately, the laboratory diagnosis of thyroid disease can be difficult because of altered hormonal states such as pregnancy and exogenous hormones. Thyroid hormones act in target tissues by binding to nuclear receptors, which induce change in gene expression (60). Extrathyroidal conversion of thyroxine (T_4) to triiodothyronine (T_3) takes

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place in target tissue. T_3 binds the nuclear receptor with higher affinity than T_4 , which makes T_3 more biologically active. Pituitary thyroid stimulating hormone (TSH) and hypothalamic thyrotropin-releasing hormone (TRH) regulate hormone production and thyroid growth by normal feedback physiology. Thyroid-stimulating immunoglobulins (TSI), once known as long-acting thyroid stimulator (LATS), bind to the TSH receptor, which results in hyperthyroid Graves' disease.

Table 9.14 Commonly Used Oral Hypoglycemic Agents

OHA	Trade Name	Daily Dose	Duration of Action (Hrs)
Glyburide	<i>Glucotrol</i>	2.5–20 mg variable dose	10–24
Glipizide sustained release	<i>Glucotrol XL</i>	2.5–20 mg once daily	24
Glimepiride	<i>Amaryl</i>	1–8 mg once or divided	12–24
Metformin	<i>Glucophage</i>	500 mg–2.5 grams in two or three divided doses	6–12
Pioglitazone	<i>Actos</i>	15–45 mg once daily	24
Rosiglitazone	<i>Avandia</i>	4–8 mg once or divided	24
Nateglinide	<i>Starlix</i>	60–120 mg before meals	2–4
Repaglinide	<i>Prandin</i>	0.5–4 mg before meals	2–4
Acarbose	<i>Precose</i>	25–100 mg before meals	2–4

OHA, oral hypoglycemic agent.

More than 99% of circulating T₄ and T₃ concentrations are bound by plasma proteins, predominately to thyroxine-binding globulin (TBG), and the remaining 1% of thyroid hormones are free. Free levels of thyroid hormones remain constant despite physiologic or pharmacologic alterations. Regardless of total serum protein levels, active thyroid hormone remains stable. In healthy women, transitions from puberty to menopause do not alter free thyroid hormone concentrations. Excess endogenous or exogenous sources of estrogen increase TBG plasma concentration by decreasing hepatic clearance. Androgens (especially testosterone) and corticosteroids have the opposite effect by increasing hepatic TBG clearance.

Thyroid function tests may be misleading in women receiving exogenous sources of estrogen because of altered binding characteristics. In euthyroid individuals, elevations of thyroid hormone concentrations arise from three mechanisms: (i) increased protein binding because of altered albumin and estrogen states, (ii) decreased peripheral conversion of T₄ to T₃, or (iii) congenital tissue resistance to thyroid hormones, which is rare. Hormonal replacement therapy and pregnancy alter laboratory findings and complicate interpretation of thyroid function studies. Most laboratories compensate by reporting a free T₄ level that mathematically corrects for physiologic alterations. If questions arise, a clinical pathologist should be consulted.

Hypothyroidism

Overhypothyroidism occurs in 2% of women, and at least an additional 5% develop subclinical hypothyroidism. This is especially true in the elderly, in whom many of the signs and symptoms are subtle. The principal cause of hypothyroidism is autoimmune thyroiditis (Hashimoto's thyroiditis). A familial predisposition is observed in many cases, but the specific genetic or environmental trigger is unknown. The incidence of autoimmune thyroiditis increases with age, affecting up to 15% of women older than 65 years.

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Many have subclinical hypothyroidism, which is defined as an elevated serum TSH concentration with a normal serum free T₄ level. It is uncertain whether treatment will improve quality of life in otherwise healthy patients who have subclinical hypothyroidism (61). Autoimmune thyroiditis may be associated with other endocrine (e.g., type 1 diabetes, primary ovarian failure, adrenal insufficiency, and hypoparathyroidism) and nonendocrine (e.g., vitiligo and pernicious anemia) disorders (62). Therefore, when autoimmune diseases are present, there should be a high degree of suspicion for concurrent thyroid disorders. Iatrogenic causes of hypothyroidism occur after surgical removal or radioactive iodine therapy for hyperthyroidism or thyroid cancer. Radiation was used to treat acne and other dermatologic disorders 45 years ago; patients undergoing such treatment have an increased risk of thyroid cancer and require close monitoring. Hypothyroidism rarely occurs secondary to pituitary or hypothalamic diseases from TSH or TRH deficiency, but this must be considered if symptoms occur after neurosurgical procedures.

Clinical Features

Manifestations of hypothyroidism include a broad range of signs and symptoms: fatigue, lethargy, cold intolerance, nightmares, dry skin, hair loss, constipation, periorbital carotene deposition (causing a yellow discoloration), carpal tunnel syndrome, weight gain (usually less than 5–10 kg), depression, irritability, and impaired memory. Menstrual dysfunction is common, either as menorrhagia

or amenorrhea. Infertility may arise from anovulation, but exogenous thyroid hormone is not useful for anovulatory euthyroid women. Empirical use of thyroid extract, which was common many years ago, should be discouraged.

Hypothyroidism is not a cause of premenstrual syndrome (PMS), but worsening PMS may be a subtle manifestation of hypothyroidism (63). Hypothyroidism may cause precocious or delayed puberty. Hyperprolactinemia and galactorrhea are unusual manifestations of hypothyroidism; however, assessment of thyroid function should be considered. To distinguish primary hypothyroidism from a prolactin-secreting pituitary adenoma, TSH levels should be assessed in women who have amenorrhea, galactorrhea, and hyperprolactinemia.

Diagnosis

Suspected hypothyroidism should always be confirmed with laboratory studies. Primary hypothyroidism is characterized by the combination of an elevated serum TSH with a low serum free T₄ level. Autoimmune thyroiditis can be confirmed by the presence of serum antithyroid peroxidase (formerly referred to as antimicrosomal) antibodies. Central hypothyroidism, although rare, is distinguished by a low or low-normal serum free T₄ level with either a low or inappropriate normal serum TSH concentration.

Therapy

Synthetic L-thyroxine (T₄) is the treatment of choice for hypothyroidism and is available as generic *levothyroxine* or *Synthroid*®, *Levoxyl*®, or *Unithroid*®. The mode of action is by conversion of T₄ to T₃ in peripheral tissues. *Levothyroxine* should be taken on an empty stomach. Absorption may be poor when taken in combination with aluminum hydroxide (common in antacids), *cholestyramine*, ferrous sulfate, or fatty meals. The usual T₄ requirement is weight related (approximately 1.6 µg/kg) but decreases for the elderly. Normal daily dosage is 0.1 to 0.15 mg but should be adjusted to maintain TSH levels within the normal range. TSH levels should be checked in 6 weeks when dosages or brands are changed. In the early 1980s, many clinicians thought that increasing the serum T₄ to mildly elevated levels would enhance conversion of T₄ to T₃. Subsequent data have proven that even a mild increase of T₄ was associated with cortical bone loss and atrial fibrillation, particularly in older women (64). A low initial T₄ dose (0.025 mg/day) should be initiated in the elderly

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or patients with known or suspected coronary artery disease. Rapid replacement may worsen angina and in some cases induce myocardial infarction.

Hyperthyroidism

Hyperthyroidism affects 2% of women during their lifetime, most often during their childbearing years. Graves' disease represents the most common disorder; it is associated with orbital inflammation causing the classic exophthalmus associated with the disease and a characteristic dermopathy, pretibial myxedema. The etiology of Graves' disease in genetically susceptible women is unknown. Autonomously functioning benign thyroid neoplasias are less common causes of hyperthyroidism and are associated with toxic adenomas and toxic multinodular goiter. Transient thyrotoxicosis may be the result of unregulated glandular release of thyroid hormone in postpartum (painless, silent, or lymphocytic) thyroiditis and subacute (painful) thyroiditis. Other rare causes of thyroid overactivity include hCG-

secreting choriocarcinoma, TSH-secreting pituitary adenoma, and struma ovarii. Factitious ingestion or iatrogenic overprescribing should be considered in patients with eating disorders.

Clinical Features

Symptoms of thyrotoxicosis include fatigue, diarrhea, heat intolerance, palpitations, dyspnea, nervousness, and weight loss. In young patients there may be paradoxical weight gain from an increased appetite. Thyrotoxicosis may cause vomiting in pregnant women, which may be confused with hyperemesis gravidarum (65). Tachycardia, lid lag, tremor, proximal muscle weakness, and warm moist skin are classic physical findings. The most dramatic physical changes are ophthalmologic and include lid retraction, periorbital edema, and proptosis. These eye findings, however, occur in less than one third of women. In elderly adults, symptoms are often more subtle, with presentations of unexplained weight loss, atrial fibrillation, or new onset angina pectoris (66). Menstrual abnormalities span from regular menses to light flow to anovulatory menses and associated infertility. Goiter is common in most younger women with Graves' disease, but may be absent in older women. Toxic nodular goiter is associated with nonhomogeneous glandular enlargement, whereas in subacute thyroiditis the gland is tender, hard, and enlarged.

Diagnosis

Most thyrotoxic patients have elevated total and free T_4 and T_3 concentrations

(measured by radioimmune assay). In thyrotoxicosis, serum TSH concentrations are virtually undetectable, even with very sensitive assays (sensitivity measured to 0.1 units). Sensitive serum TSH measurements may aid in the diagnosis of hyperthyroidism. Radioiodine uptake scans are useful in the differential diagnosis of established hyperthyroidism. Scans with homogeneous uptake of radioactive iodine are suggestive of Graves' disease, whereas heterogeneous tracer uptake is suggestive of a diagnosis of toxic nodular goiter. In distinction, thyroiditis and medication-induced thyrotoxicosis have diminished glandular radioisotope concentration.

Therapy

Antithyroid medications, either *propylthiouracil* (PTU 50–300 mg every 6–8 hours) or *methimazole* (10–30 mg per day) are used for initial therapy. After metabolic control is obtained, definitive therapy is obtained by thyroid ablation with radioiodine, which results in permanent hypothyroidism. Both antithyroid drugs block thyroid hormone biosynthesis and may have additional immunosuppressive effects on the gland. The primary difference in oral medications is that PTU partially inhibits extrathyroidal T_4 -to- T_3 conversion,

whereas *methimazole* does not. However, *methimazole* has a longer half-life and permits single daily dosing, which may encourage compliance. Euthyroidism is typically restored in 3 to 10 weeks, and treatment with oral antithyroid agents is continued for 6 to 24 months, unless total ablation with radioiodine or surgical resection is performed. Surgery

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has become less popular because it is invasive and may result in inadvertent parathyroid removal, which commits the patient to lifelong calcium therapy.

The relapse rate with oral antithyroid medications is 50% over a lifetime. Lifelong follow-up is important when medical therapy is used solely because of the high relapse rate. Both medications have infrequent (5%) minor side effects, which include fever, rash, or arthralgias. Major toxicity (e.g., hepatitis, vasculitis, and agranulocytosis) occurs in less than

1%. Agranulocytosis cannot be predicted by periodic complete blood counts; therefore, patients who have sore throats or fevers should stop taking medication and call their physician immediately.

Therapy with iodine-131 provides a permanent cure of hyperthyroidism in 90% of patients.

The principal drawback to radioactive iodine therapy is the high rate of postablative hypothyroidism, which occurs in at least 50% of patients immediately after therapy with additional cases developing at a rate of 2% to 3% per year. Based on the assumption that hypothyroidism will develop, patients should be given lifetime thyroid replacement.

Beta-adrenergic blocking agents such as *propranolol* or *atenolol* are useful adjunctive therapy for control of sympathomimetic symptoms such as tachycardia (67). An additional benefit of beta-blockers is the blocking of peripheral conversion of T₄ to T₃. In rare cases of thyroid storm, PTU, beta-blockers, glucocorticoids, and high-dose iodine preparations (intravenous sodium iodide) should be administered immediately, and referral to an intensive care unit is advisable.

Thyroid Nodules and Cancer

Thyroid nodules are common and found on physical examination in up to 5% of patients. Nodules may be demonstrated on ultrasound in approximately 50% of 60-year-old persons.

The vast majority of nodules when discovered are asymptomatic and benign; however, malignancy and hyperthyroidism must be excluded (68). Ultrasound-guided fine-needle aspiration is recommended in the presence of the following factors: history of radiation to the head, neck, or upper chest, family history of thyroid cancer, ultrasound findings suggestive of malignancy, or a nodule larger than 1.5 cm in diameter (69).

Thyroid function tests should be performed before fine-needle aspiration and, if results are abnormal, the underlying disease should be treated.

Because most nodules are "cold" on scanning, it is more cost-effective to proceed with tissue sampling rather than scanning. Biopsy is successful and provides a diagnosis in 95% of cases; however, in the 5% of patients in whom the diagnosis cannot be established, surgical biopsy is necessary. Only 20% of surgical biopsies of an "indeterminate aspiration" are found to be malignant (70). Lesions that are confirmed malignant on biopsy should be treated with surgery, and benign nodules should be palpated every 6 to 12 months. *Thyroxine* suppressive therapy for benign nodules is not recommended (69).

Papillary thyroid carcinoma is the most common malignancy, found in 75% of cases.

Patients younger than 50 years of age with a primary tumor of less than 4 cm at presentation, even with associated cervical lymph node metastasis, are usually cured. In the elderly, anaplastic tumors have a poor prognosis and progress rapidly despite therapy.

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10

Family Planning

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- **The most common methods of contraception used in the United States are sterilization, oral contraceptives, and condoms, in that order.**
- **Latex condoms and other barriers reduce the risk of sexually transmitted diseases (STDs) and cervical cancer.**
- **The two intrauterine devices (IUDs) available in the United States, the *copper T380A (ParaGard)* and the *levonorgestrel T (Mirena)*, are as effective as tubal sterilization and are associated with long-term risk of pelvic infection that is no greater than that in the general population.**
- **The combination estrogen–progestin oral contraceptives, patch, and vaginal ring all provide excellent contraception when used correctly, and all increase the risk of venous thrombosis and thromboembolism.**
- **Present low-dose estrogen–progestin combinations do not increase the risk of heart attack among nonsmokers younger than age 35 years who have no other risks for vascular disease.**

- **Oral contraceptives do not increase the risk of breast cancer.**
- **Use of progestin-only injectable and implant hormonal contraceptives results in very low pregnancy rates without the estrogen-associated risk of thrombosis.**
- **Hormonal contraceptives provide extensive contraceptive and noncontraceptive health benefits, including reduced risk for endometrial and ovarian cancer.**
- *Levonorgestrel 1.5 mg (Plan B) is the most effective hormonal means of emergency contraception. Efficacy is greatest within 24 hours of intercourse but is still high at 5 days. Emergency contraception with the copper T 380A IUD is highly effective up to 7 days after intercourse.*
- **Safe, long-term contraception is provided with laparoscopy and bipolar electrocautery application to three adjacent sites on each tube, the Silastic band, or the *Filshie clip*.**

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- **Hysteroscopic insertion of the *Essure* system provides highly effective permanent sterilization for women without the use of general anesthesia or abdominal incision.**
- **Vasectomy provides highly effective, low-cost sterilization for men and is associated with neither heart disease nor prostate cancer.**
- **Abortion mortality rates fell rapidly with legalization; currently, the overall mortality risk is less than 1 per 100,000, well below the maternal mortality rate.**
- **The risk of abortion mortality increases with gestational age, from 0.1 per 100,000 at 8 weeks or less, but even at 16 to 20 weeks, abortion is safer than continuing pregnancy.**

The history of contraception is a long one, dating to ancient times; however, the voluntary control of fertility is even more important in modern society (1). With each woman expected to have no more than one or two children, most of her reproductive years are spent trying to avoid pregnancy. Effective control of reproduction is essential to a woman's ability to accomplish her individual goals. From a larger perspective, the rapid growth of the human population in this century threatens the survival of all. **At its present rate, the population of the world will double in 54 years, and that of many of the poorer countries of the world will double in about 20 years** (2) (Fig. 10.1). **For the individual and**

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for the planet, reproductive health requires careful use of effective means to prevent both pregnancy and sexually transmitted diseases (STDs) (3).

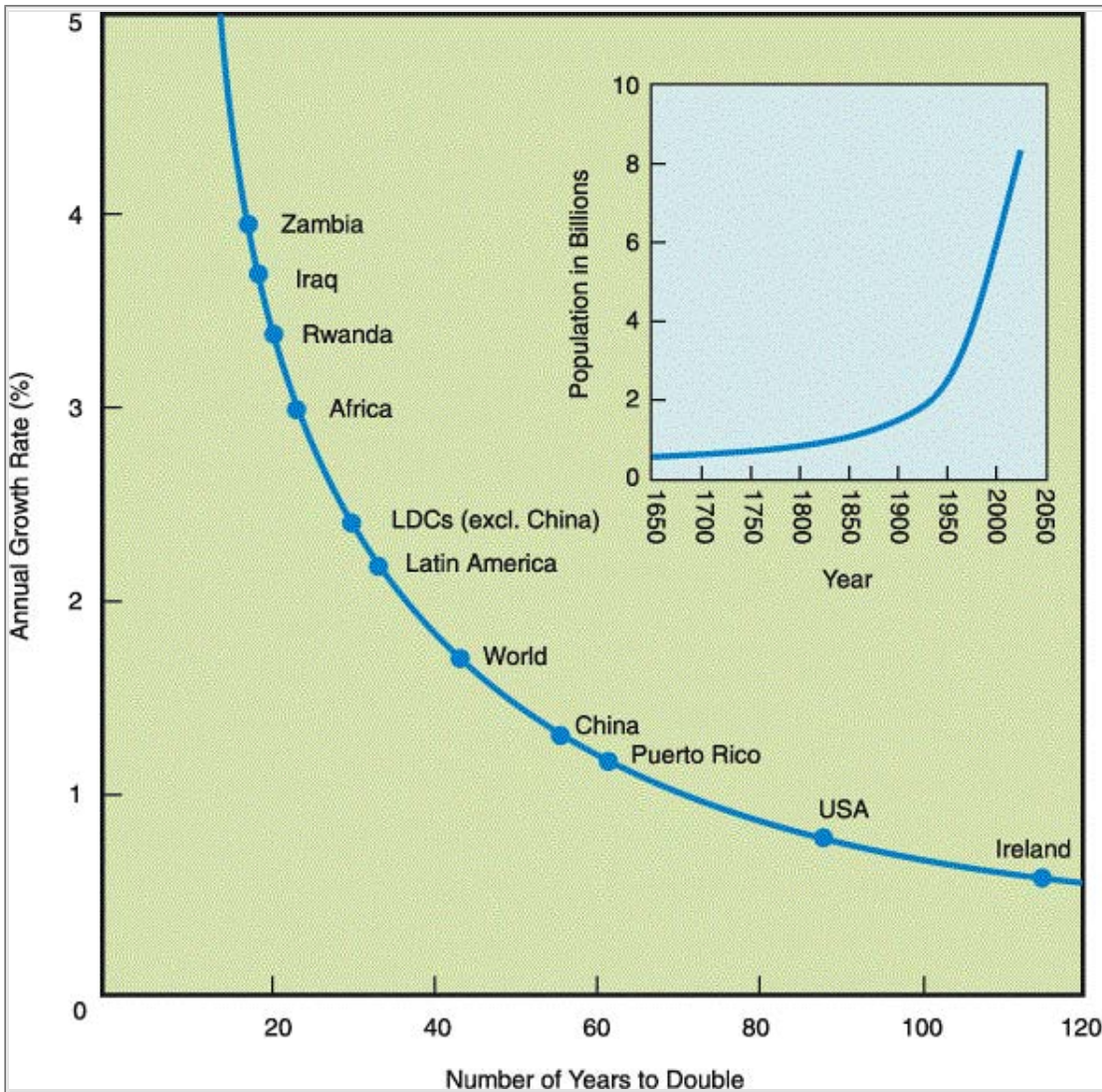


Figure 10.1 Doubling time at different rates of population growth, with representative countries, and world population growth curve. (From Hatcher RA, Trussell J, Stewart F, et al. Contraceptive technology. 18th ed. New York, NY: Ardent Media, 2004: 764, with permission.)

Table 10.1 Number of Women 15 to 44 Years of Age and Percent Distribution by Current Contraceptive Status and Method, United States 1982, 1995, and 2002

	1982	1995	2002
All women	54,099,000	60,201,000	61,561,000
Using contraception %	55.7	64.2	61.9
Female sterilization	12.9	17.8	16.7
Male sterilization	6.1	7.0	5.7
Pill	15.6	17.3	18.9
Implant, Lunelle™ or patch	NA	0.9	0.8
3-month injectable (DepoProvera)	NA	1.9	3.3
Intrauterine device	4.0	0.5	1.3
Condom	6.7	13.1	11.1
Periodic abstinence—calendar rhythm	1.8	1.3	0.7
Periodic abstinence—natural family planning	0.3	0.2	0.2
Withdrawal	1.1	2.0	2.5

Other methods ^a	2.7	1.1	0.6
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^aOther methods include Today sponge, cervical cap, and female condom.
Source: **Mosher WD, Martinez GM, Chandra A, et al.** Uses of contraception and use of family planning services in the United States: 1982–2002. *Adv Data* 2004; 350: 17.

From puberty until menopause, women are faced with concerns about childbearing or its avoidance: The only options are sexual abstinence, contraception, or pregnancy.

The contraceptive choices made by couples in the United States in 2002, when the last national fertility survey of a large national probability sample was conducted by the government, are shown in Table 10.1 (4). The oral contraceptive was first choice, used by 18.9% of women aged 15 to 44 years. Female sterilization was second choice, used by 16.7%. However, with the addition the 5.7% of couples relying on male sterilization, 22.4% of couples were relying on sterilization, making this the first choice of contraception. Condoms were third choice, used by 11.1%. Oral contraceptive use declines with age, and the rate of sterilization increases. As a result, 41% of women younger than 35 to 39 years and 50% of women aged 40 to 44 years have had female sterilization. About 10% of women used more than one method of contraception. Condoms were the second most common method. **Although use of contraception is high, a significant proportion of sexually active couples (7.4%) do not use contraception, and each year, two of every 100 women aged 15 to 44 years have an induced abortion** (4,5). Abortion is an obvious indicator of unplanned pregnancy. Abortion ratios by age group indicate that the use of abortion is greatest for the youngest women and least for women in their late 20s and early 30s (Fig. 10.2). Use increases as women age. **Young women are much more likely to experience unplanned pregnancy because they are more fertile than older women and because they are more likely to have intercourse without contraception.** The effect of age on pregnancy rates with different contraceptive methods is shown in Figure 10.3.

Efficacy

Factors affecting whether pregnancy will occur include the fecundity of both partners, the timing of intercourse in relation to the time of ovulation, the method of contraception used,

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the intrinsic effectiveness of the contraceptive method, and the correct use of the method. It is impossible to assess the effectiveness of a contraceptive method in isolation from the other factors. The best way to assess effectiveness is long-term evaluation of a group of sexually active women using a particular method for a specified period to observe how frequently pregnancy occurs. **A pregnancy rate per 100 women per year can be calculated using the Pearl formula (dividing the number of pregnancies by the total number of months contributed by all couples, and then multiplying the quotient by 1,200).** With most methods, pregnancy rates decrease with time as the more fertile or less careful couples become pregnant and drop out of the calculations. **More accurate information is provided by the life-table method. This method calculates the probability of pregnancy in successive months, which are then added over a given interval.** Problems relate to which pregnancies are counted: those occurring among all couples or those in women the investigators deem to have used the method correctly. Because of this complexity, rates of pregnancy with different methods are best calculated by reporting two different rates derived from multiple studies (i.e., the lowest rate) and the usual rate as shown in Table 10.2.

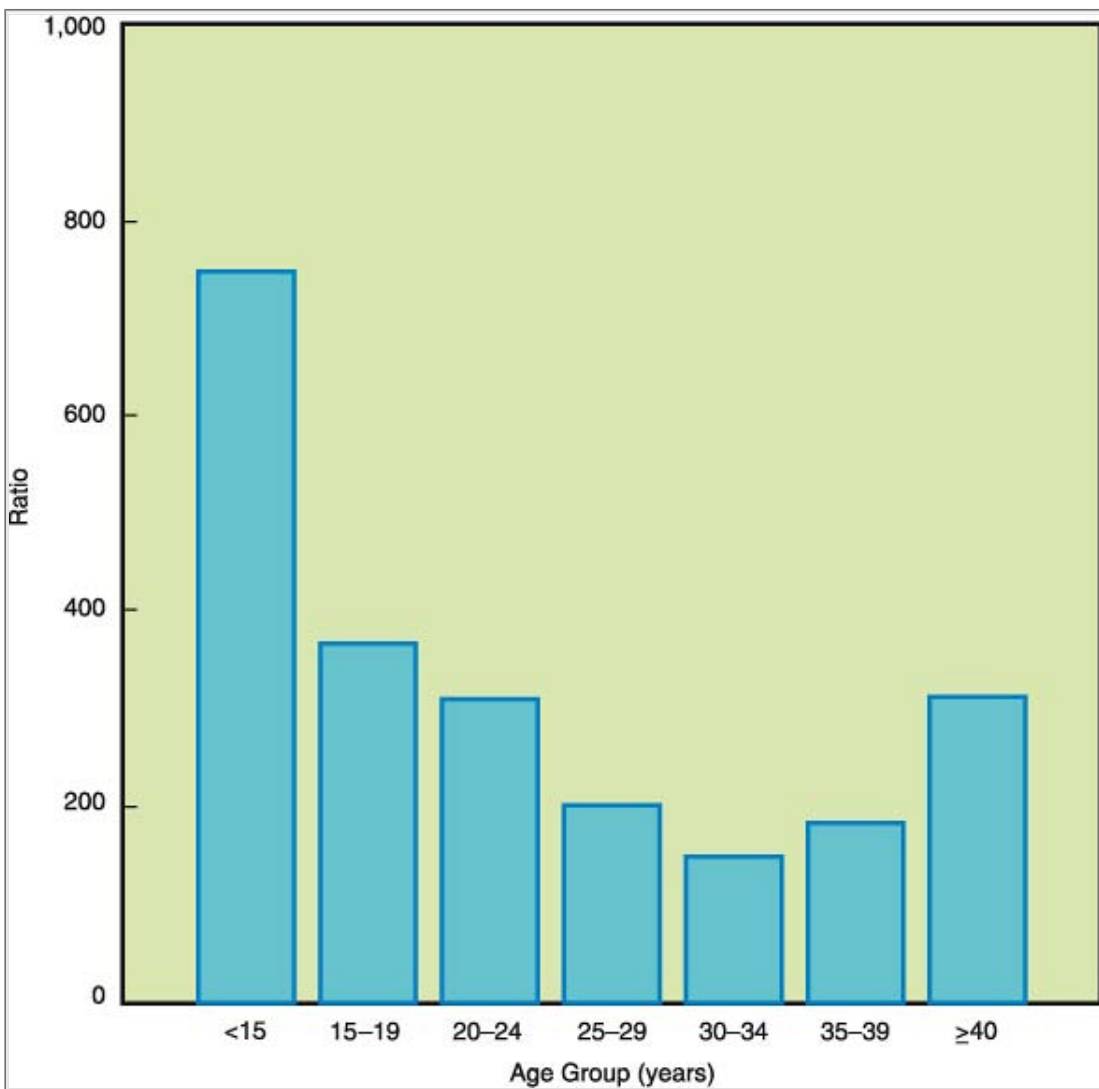


Figure 10.2 Abortion ratios, by age groups — United States, 1973–2001. Ratio of induced abortions per 1,000 live births. (From **Strauss LT, Herndon J, Chang J, et al.** Abortion surveillance, United States 2001. *MMWR Surveill Summ* 2004;53[SS-9]:11.)

Safety

Some contraceptive methods have associated health risks; areas of concern are listed in Table 10.3. All of the methods are safer than the alternative (pregnancy with birth), with the possible exception of oral contraceptive (OC) use by women older than 35 years of age

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who smoke (6). **Most methods provide noncontraceptive health benefits in addition to contraception. Oral contraceptives reduce the risk of ovarian and endometrial cancer and ectopic pregnancy. Barrier methods provide some protection against STDs, cervical cancer, and tubal infertility.**

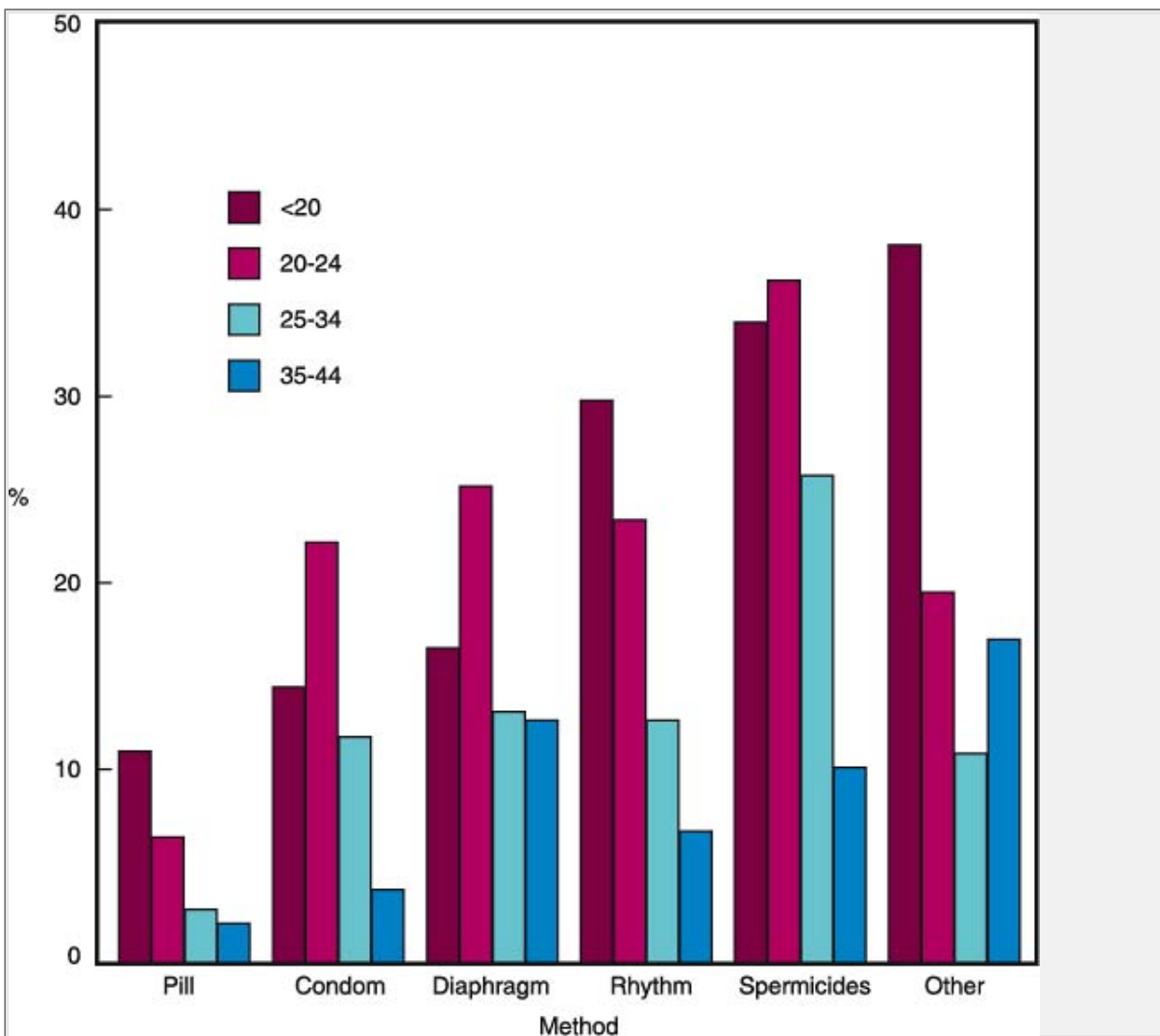


Figure 10.3 Percentage of women experiencing an accidental pregnancy, in the first 2 years of use, according to method, combined 1988 and 1995 National Survey of Family Growth. (From Ranjit N, Bankole A, Forrest JD, et al. Contraception failure in the first two years of use: differences across socioeconomic subgroups. *Fam Plann Perspect* 2001; 33:25 [Table 6], with permission.)

Cost

Some methods, such as intrauterine devices (IUDs) and subdermal implants, require an initial high investment but provide prolonged protection for a low annual cost. The results of a complex cost analysis based on the cost of the method plus the cost of pregnancy if the method fails are shown in Table 10.4. **Sterilization and the long-acting methods are the least expensive over the long term (7).**

Nonhormonal Methods

Coitus Interruptus

Coitus interruptus is withdrawal of the penis from the vagina before ejaculation. This method, along with induced abortion and late marriage, is believed to account for most of the decline in fertility of preindustrial Europe (8). Coitus interruptus remains

a very important means of fertility control in many countries. Eighty-five million couples are estimated to use the method worldwide, yet it has had little recent formal study. This method has obvious advantages: immediate availability and no cost. The penis must be completely withdrawn both from the vagina and from the external genitalia. Pregnancy has occurred from ejaculation on the female external genitalia without penetration. Coitus

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interruptus has been found to reduce transmission of human immunodeficiency virus (HIV) in couples who are mutually monogamous (9). Theoretically, some reduction of risk from other STDs would be expected, but this phenomenon does not appear to have been studied. Efficacy is estimated to range from 4 pregnancies per 100 women in the first year with perfect use to 27 per 100 with typical use (Table 10.2).

Method	Women Experiencing Accidental Pregnancy within the First Year of Use %		Women Continuing Use at 1 Year (%)
	Typical Use	Perfect Use	
No method	85	85	
Spermicides	29	18	42
Periodic abstinence	25		67
Calendar		9	
Ovulation method		3	
Symptothermal		2	
Postovulation		1	
Withdrawal	27	4	43
Cap			
Parous women	32	26	46
Nulliparous women	16	9	57
Sponge			
Parous women	32	20	46
Nulliparous women	16	9	57
Diaphragm	16	6	57
Condom			
Female (Reality)	21	5	49
Male	15	2	53
Combined pill and progestin-only pill	8	0.3	68
Patch (Evra™)	8	0.3	68
NuvaRing	8	0.3	68
Intrauterine devices			
ParaGard™ (Copper T 380A)	0.8	0.6	78
Myrena (levonorgestrel T)	0.1	0.1	81
DepoProvera	3	0.3	70
Lunelle	3	0.05	56
Norplant ^a and Norplant II	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

^a Cumulative 5-year pregnancy rate for pliable tubing, divided by 5.

From **Hatcher RA, Trussell J, Stewart F, et al.** *Contraceptive technology*. 18th ed.

New York, NY: Ardent Media, Inc., 2004:226, with permission.

Table 10.3 Overview of Contraceptive Methods

Method	Advantages	Disadvantages	Risks	Noncontraceptive Benefits
Coitus interruptus	Available, free	Depends on male control	Pregnancy	Decreased HIV risk
Lactation	Available, free	Unreliable duration of effect	Pregnancy	Decreased breast cancer
Periodic abstinence	Available, free	Complex methodology; motivation is essential	Pregnancy	None
Condoms	Available, no prescription needed	Motivation is essential; must be used each time; depends on man	Pregnancy	Proven to decrease STDs and cervical cancer
Spermicides and sponge	Available, no prescription needed	Must be used each time	Pregnancy	None
Diaphragm/cap	Nonhormonal	Must be used each time; fitting required	Pregnancy, cystitis	Proven to decrease STDs and cervical cancer
ParaGard IUD	High efficacy for 10 years, unrelated to coitus	Initial cost; skilled inserter; pain and bleeding	Initial mild risk for PID and septic abortion	None
Mirena IUD	High efficacy for 5 years; unrelated to coitus	Initial cost; skilled inserter; amenorrhea for some	Initial mild risk for PID and septic abortion	Reduced bleeding; can be used to treat menorrhagia
Oral contraceptives Evra™ patch NuvaRing	High efficacy	Motivation to take daily; cost	Thrombosis; older smokers have increased risk of MI and stroke	Many benefits (see text)
DMPA	High efficacy, convenience	Injection required; bleeding pattern Osteopenia Weight gain	Probably none	Many (see text)
Lunelle™	High efficacy, convenience	Monthly injection	Probably same as orals	Probably same as orals
Implants	High efficacy, convenience	Surgical insertion and removal; initial cost; bleeding pattern	Functional cysts	Unknown
Emergency contraception Levonorgestrel	Moderate efficacy	Frequent use disrupts menses	None	Unknown

HIV, human immunodeficiency virus; IUD, intrauterine device; PID, pelvic inflammatory disease; MI, myocardial infarction; DMPA, depomedroxyprogesterone acetate.

Breastfeeding

Breastfeeding can be used as a form of contraception and can be effective depending on individual variables. The use of contraception during lactation should take into consideration the women's needs as well as the need to maintain lactation.

Table 10.4 Cost per Patient per Year of Contraceptive Methods

Method	Cost (\$)	Cost Multiple (\$) ^a
Vasectomy	55	1.0
Tubal ligation	118	2.14
Intrauterine device	150	2.71
Norplant	202	3.66
Depomedroxyprogesterone acetate	396	7.19
Oral contraceptives	456	8.27
Condoms	776	14.08
Diaphragm	1,147	20.81

^aFor every \$1.00 spent on vasectomy, the amount shown would be spent on the method indicated.

From **Ashraf T, Arnold SB, Maxfield M**. Cost effectiveness of levonorgestrel subdermal implants: comparison with other contraceptive methods available in the United States. *J Reprod Med* 1994; 39: 791–798, with permission.

Lactation Amenorrhea

Ovulation is suppressed during lactation. The suckling of the infant elevates prolactin levels and reduces gonadotropin-releasing hormone (GnRH) from the hypothalamus, reducing luteinizing hormone (LH) release and thus inhibiting follicular maturation (10). The duration of this suppression is variable and is influenced by the frequency and duration of nursing, length of time since birth, and probably by the mother's nutritional status. Even with continued nursing, ovulation eventually returns but is unlikely before 6 months, especially if the woman is amenorrheic and is fully breastfeeding with no supplemental foods given to the infant (11). For maximum contraceptive reliability, feeding intervals should not exceed 4 hours during the day and 6 hours at night, and supplemental feeding should not exceed 5% to 10% of the total amount of feeding (12). Six-month pregnancy rates of 0.45% to 2.45% have been reported for couples relying solely on this method (13). To prevent pregnancy, another method of contraception should be used from 6 months after birth, or sooner if menstruation resumes. **Breastfeeding reduces the mother's lifetime risk of breast cancer.** In a very large study in Korea, 13 to 24 months of lactation reduced the risk of breast cancer by 30%, and there was a clear trend of decreasing breast cancer risk with increasing duration of lactation (14).

Contraception during Lactation

Use of combination OCs generally is not advised during lactation because they reduce the amount and quality of breast milk. Combination OCs can be used after 6 weeks, once milk production is established. **Progestin-only OCs, implants, and injectable contraception do not affect milk quality or quantity** (12). Labeling of the U.S. Food and Drug Administration (FDA) and guidelines from the American College of Obstetricians and Gynecologists suggest that progestin-only OCs can be started 2 to 3 days postpartum, whereas depot medroxyprogesterone acetate (Depo Provera) injections or implants can begin at

6 weeks. These recommendations are not based on any observed adverse effect of early administration (12), and many maternity programs begin injectable contraception with progestin at the time of hospital discharge. Barrier methods, spermicides, and the *copper T380A IUD (ParaGard)* are also good options for nursing mothers. Because levonorgestrel implants have no adverse effect on breastfeeding, none should be expected from the *levonorgestrel T IUD*, which releases *levonorgestrel* but is associated with lower blood levels than the implants.

Fertility Awareness

Periodic abstinence, also described as "natural contraception" or "fertility awareness," requires avoiding intercourse during the fertile period around the time of ovulation. A variety of methods are used: the calendar method, the mucous method (Billings or ovulation method), and the symptothermal method, which is a combination of the first two methods. With the mucous method, the woman attempts to predict the fertile period by feeling the cervical mucus with her fingers. Under estrogen influence, the mucus increases in quantity and becomes progressively more slippery and elastic until a peak day is reached. The mucus then becomes scant and dry under the influence of progesterone until onset of the next menses. Intercourse may be allowed during the "dry days" immediately after menses until mucus is detected. Thereafter, the couple must abstain until the fourth day after the "peak" day.

In the symptothermal method, the first day of abstinence is predicted either from the calendar, by subtracting 21 from the length of the shortest menstrual cycle in the preceding 6 months, or the first day mucus is detected, whichever comes first. The end of the fertile period is predicted by use of basal body temperature. The woman takes her temperature every morning and resumes intercourse 3 days after the thermal shift, the rise in body temperature that signals that the corpus luteum is producing progesterone and that ovulation has occurred. The postovulatory method is a variation in which the couple has intercourse only after ovulation is detected.

A system of hormone monitoring designed to better define the fertile period involves placement of disposable test sticks in a small battery-powered device to detect urinary estrone-3 glucuronide and LH. This device (*Persona* or *Clear Plan Easy Fertility Monitor*) can serve as both an aid to fertility and a form of contraception (15).

Efficacy

Efforts to study the effectiveness of fertility awareness with randomized trials have proven frustrating because of the very high dropout rate of the subjects despite intensive training and ongoing support. Nonetheless, the ovulation method was evaluated by the World Health Organization in a five-country study. Women who successfully completed three monthly cycles of teaching were then enrolled in a 13-cycle efficacy study. There was a 3.1% probability of pregnancy in 1 year for the small proportion of couples who used the method perfectly and 86.4% probability of pregnancy for the rest (16). A review of 15 national surveys from developing countries estimated a 12-month gross failure rate of 24 pregnancies per 100 (17). The personal hormone-monitoring device has been tested in a three-country study of 710 women. The pregnancy rate was 12.1% over a 13-cycle interval. Despite the pregnancies, the continuation rate was 78% after 13 cycles (15).

Because sperm may survive 5 to 7 days in the female genital tract, even a week's abstinence around the time of actual ovulation offers no guarantee against pregnancy. Also, ovulation can occur even in the absence of menstruation. Pregnancies have occurred after a single act of coitus 7 days before apparent ovulation indicated by basal body temperature. Vaginal infections increase vaginal discharge, complicating the

detection of preovulatory mucus.

Risks

Conceptions resulting from intercourse remote from the time of ovulation more often lead to spontaneous abortion than conceptions from midcycle intercourse (18). However, malformations are not more common (18).

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Condoms

In the 1700s, condoms made of animal intestine were used by the aristocracy of Europe, but condoms were not widely available until the vulcanization of rubber in the 1840s (1). Modern condoms are usually made of latex rubber, although condoms made from animal intestine are still sold and are preferred by some who feel they afford better sensation. Until recently, condoms in the United States were made with a relatively thick wall (0.065–0.085 mm) to prevent breakage. Japanese condoms as thin as 0.02 mm are now available in the United States (2). New condoms made from nonlatex materials such as polyurethane or synthetic elastomers that are thin, odorless, transparent, and transmit body heat also are available. Although the nonlatex condoms may break more easily than the latex varieties, substantial numbers of study participants preferred them and would recommend them to others (19).

Condoms prelubricated with the spermicide *nonoxynol-9* are more effective than condoms without spermicide (20). The risk of condom breakage is about 3% (21) and is related to friction. Use of water-based lubricants may reduce the risk of breakage. Petroleum-based products such as mineral oil must be avoided because even brief exposure to them markedly reduces the strength of condoms (22).

Sexually Transmitted Diseases

Latex condoms and other barrier methods reduce the risk of STDs. Gonorrhea, ureaplasma, and pelvic inflammatory disease (PID) and its sequel (tubal infertility) are reduced with consistent use of barrier methods (23,24). A comparison of infertile women with postpartum women showed a 40% reduction in infertility with use of condoms or the diaphragm (25). Tested *in vitro*, *Chlamydia trachomatis*, herpes virus type 2, human immunodeficiency virus (HIV), and hepatitis B did not penetrate latex condoms but did cross through condoms made from animal intestine (26). Follow-up of sexual partners of HIV-infected individuals has shown that condom use provides considerable protection (27). Consistent condom use provides more protection than inconsistent use (28,29). In one study, couples who use condoms 0% to 50% of the time had an HIV seroconversion rate of 20.8 per 100 couple years, whereas those who used condoms 100% of the time had a conversion rate of only 2.3 per 100 couple years (29). ***Nonoxynol-9* should not be used with condoms for HIV protection because it has been associated with genital lesions.** *Nonoxynol-9* does not add to the protection afforded by condoms alone (29,30).

Condoms also offer protection from cervical neoplasia. In one study, the relative risk of severe dysplasia among users of condoms or diaphragms was 0.4 at 5 to 9 years of use and only 0.2 when the barriers had been used for 10 years or more, a 60% to 80% reduction (31). Another study compared women with invasive cervical cancer to controls. The relative risk for invasive cervical cancer was 0.4 when those who had used condoms or diaphragms were compared with those who had never used them (32). The presumed mechanism of protection is reduced transmission of human papillomavirus (HPV).

Latex allergy could lead to life-threatening anaphylaxis in either partner from latex condoms. Nonlatex condoms of polyurethane and *Tactylon* should be offered to couples who have a history suggestive of latex allergy.

Female Condom

The female condom is a vaginal pouch made of polyurethane. It is recommended for prevention of pregnancy and STDs, including HIV. Breakage may occur less often with the female condom than the male condom; however, slippage appears to be more common, especially for those new to its use (33). Exposure to seminal fluid is slightly higher than with the male condom (34). Initial U.S. trials showed a pregnancy rate of 15% in 6 months; however, reanalysis suggests that with perfect use, the pregnancy rate may be only 2.6%. This rate is comparable to perfect use of the diaphragm and cervical cap, the other female

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barrier methods (35). As with the male condom, failure rates fall with increasing experience. Colposcopic studies of women using the female condom demonstrate no signs of trauma or change in the bacterial flora (36). However, clinical trials suggest both men and women find the female condom less acceptable than the male condom (37).

Vaginal Spermicides

Currently available vaginal spermicides combine a spermicidal chemical, either *nonoxynol-9* or *octoxynol*, with a base of cream, jelly, aerosol foam, foaming tablet, film, suppository, or a polyurethane sponge. *Nonoxynol-9* is a nonionic surface-active detergent that immobilizes sperm. In simulated intercourse under laboratory conditions, aerosol foams provided rapid dispersal throughout the vagina and offered the best protection. Jellies and melting suppositories provided poor distribution (34). ***Nonoxynol-9* spermicides alone appear considerably less effective in preventing pregnancy than condoms or diaphragms.** Women using *nonoxynol-9* spermicides frequently have higher rates of genital lesions than women not using spermicides. These lesions may increase their risk for STDs and HIV (38). In the same studies of serodiscordant couples in which condoms were proved effective in preventing transmission of HIV, *nonoxynol-9* spermicides were not effective (29).

Concerns have been raised about possible teratogenicity of spermicides. *Nonoxynol-9* is not absorbed from the human vagina, however (36,39), and several large studies have found no greater risk of miscarriage, birth defects, or low birth weight in spermicide users than in other women (40,41).

Nonoxynol-9 is toxic to the lactobacilli that normally colonize the vagina. Women who use spermicides regularly have increased vaginal colonization with the bacterium *Escherichia coli* and may be predisposed to *E. coli* bacteriuria after intercourse (42).

Vaginal Barriers

At the beginning of the 20th century, four types of vaginal barriers were used in Europe: vaginal diaphragm, cervical cap, vault cap, and Vimule. All of these barriers are still made and sold in England. Vaginal diaphragms and cervical caps are used in the United States. When used consistently, vaginal barriers can be highly effective. They are safe, and, as with condoms, they have the noncontraceptive benefit of relative protection from STDs, tubal infertility, and cervical neoplasia. Recent interest in finding alternatives to condoms for HIV prevention in high-prevalence areas has rekindled interest in vaginal barriers (43).

Diaphragm

The diaphragm consists of a circular spring covered with fine latex rubber (Fig. 10.4). There

are several types of diaphragm, as determined by the spring rim: coil, flat, or arcing. Coil-spring and flat-spring diaphragms become a flat oval when compressed for insertion. Figure 10.4 Wide-seal diaphragm. Arcing diaphragms form an arc or half moon when compressed; they are easiest to insert correctly. **The practitioner must not only fit the diaphragm for the patient, but also instruct her in its insertion and verify by examination that she can insert it correctly to cover the cervix and upper vagina.** Spermicide is always prescribed for use with the diaphragm; however, whether this practice is necessary is not well studied. In a small trial, women using the diaphragm without spermicide had a higher (19.3 per 100 woman-years) but statistically not significant risk for pregnancy than those who used the diaphragm with spermicide (12.3 per 100 woman-years) (44). Conversely, a different study found that women who wore the diaphragm constantly, removing, washing, and reinserting the diaphragm daily without using a spermicide, had lower pregnancy rates than women who used the diaphragm in the conventional fashion, with a spermicide, only when needed (45). Proper fitting and use are key to the effectiveness of the diaphragm.

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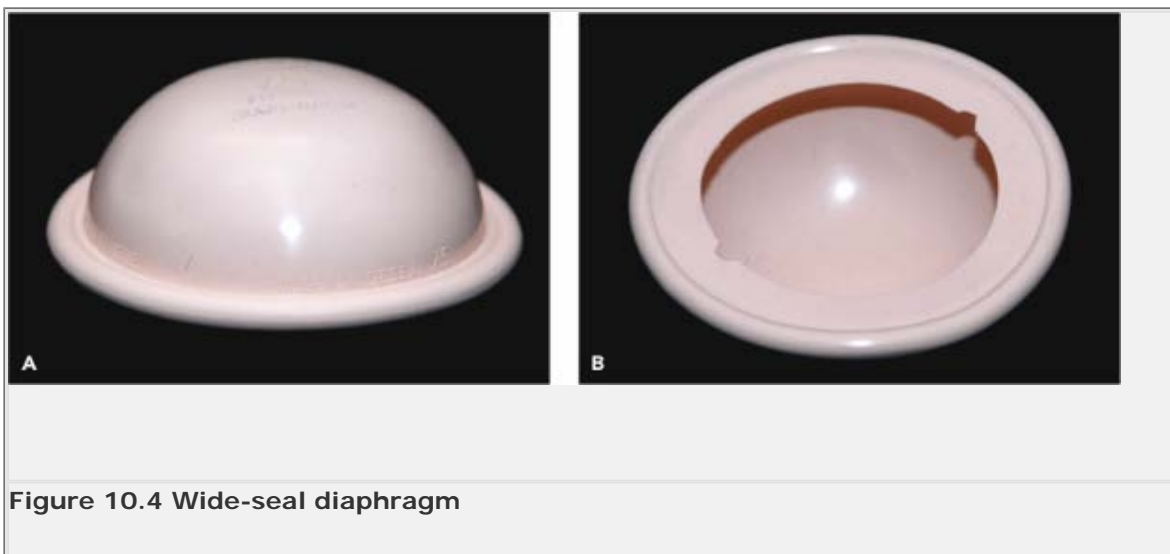


Figure 10.4 Wide-seal diaphragm

Fitting Diaphragms

Fitting of a diaphragm should be performed as follows:

- **A vaginal examination should first be performed.** With the first and second fingers in the posterior fornix, the thumb of the examining hand is placed against the first finger to mark where the first finger touches the pubic bone. The distance from the tip of the middle finger to the tip of the thumb is the diameter of the diaphragm that should first be tried.
- **A set of test diaphragms of various sizes is used, and the test diaphragm is inserted and checked by palpation.** The diaphragm should open easily in the vagina and fill the fornices without pressure. The largest diaphragm that fits comfortably should be selected. A size 65, 70, or 75 diaphragm will fit most women.
- **The patient should practice insertion and should be reexamined to confirm proper position of the device.** About 1 teaspoon of water-soluble spermicidal jelly or cream is placed in the cavity of the dome. The diaphragm is inserted with the dome downward so that the cervix will sit in a pool of the spermicide.

The diaphragm can be inserted several hours before intercourse. If intercourse is repeated, additional spermicidal jelly should be inserted into the vagina without removing the diaphragm. The diaphragm should be left in place at least 6 hours after intercourse to allow for immobilization of sperm. It is then removed, washed with soap and water, allowed to dry, and stored away from heat. It should not be dusted with talc because genital exposure to talc may increase the risk of ovarian cancer.

Risks

Diaphragm use, especially prolonged use during multiple acts of intercourse, appears to increase the risk of bladder infections. The risk of cystitis increases with the numbers of days the diaphragm is used in a week (relative risk, 1.42, 2.83, and 5.68 for use 1, 3, or 5 days in a week, respectively) (46). A smaller-sized, wide-seal diaphragm or a cervical cap can be used if recurrent cystitis is a problem, although the problem may relate not only to mechanical obstruction but also to alterations in vaginal flora produced by the spermicide. An epidemiologic study comparing cases of toxic shock with controls found no increased risk from diaphragm use (47).

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Other Barriers

The *Prentif* cervical cap made of latex rubber is no longer available in the United States. It had been in continuous use for most of the 20th century, but competition from other methods made its continued production impractical. Studies of the efficacy of the *Prentif* caps revealed a range of results. A multicenter study of 3,433 women found a first-year pregnancy rate of 11.3 per 100 women. Women whose pattern of use was described as "near perfect" had a first-year pregnancy rate of 6.1 per 100, one half that of the overall rate (48). By 1 year, 49% of women discontinued use or were lost to follow-up. In randomized trials, the cervical cap was as effective as the diaphragm overall, but the failure rates with perfect use were considerably higher for the cap than for the diaphragm (49). Parous women using the cap had more failures than nulliparous women.

The FemCap

A new version of the cervical cap made of silicone rubber was approved by the FDA in 2003. It is marketed under the name *FemCap*. It looks like a sailor's hat with the dome covering the cervix and the brim fitting into the vaginal fornices; the brim serves to form a seal against the vaginal wall, thereby acting as a funnel to direct the ejaculate fluid into the groove facing the vaginal opening, which is filled with spermicide (50). This groove could also be used for microbicides, if they are available in the future. Additionally, the *FemCap* features a small strap that facilitates removal. It is made in three sizes—22-, 26-, and 30-mm diameter — and can be expected to be reusable for 2 years. It is used with spermicide and should be left in place for at least 6 hours after intercourse; however, it may be left in place as long as 48 hours at a time. The *Femcap* requires a clinician's fitting and prescription for use.

Lea's Shield

Lea's Shield is another vaginal barrier device made of silicone rubber and recently approved by the FDA. It is shaped like an elliptical bowl with a central air valve, approximately the size of a diaphragm, featuring an anterior loop to assist its removal. The posterior end is thicker and therefore less likely to rotate when in place. It comes in one size; proper fitting requires only that it cover the cervix, sit behind the symphysis, and be comfortable. A prescription is

required (51). Safety and efficacy are similar to that of other vaginal barrier methods, and acceptability among users compares favorably. Approximately 87% of those responding to the question stated that they would recommend its use to a friend (51).

Risks

In one large trial of the *Prentif* cap, negative cervical cytology progressed to dysplasia in 4% of cap wearers and in 2% of diaphragm wearers (48). In contrast, another study found cap wearers to be protected from dysplasia when compared with controls using other methods (52). The results of cervical cytology appeared to improve during use. Cap use was associated neither with cystitis (48,52) nor with toxic shock (47).

The Sponge

The Today sponge is a polyurethane dome-shaped device containing nonoxynol-9. It is moistened with water and then inserted high in the vagina to cover the cervix. It combines the advantages of a disposable barrier with spermicide and provides protection for 24 hours. Initially introduced into the United States in 1983, it rapidly became the best-selling over-the-counter method for female contraception. It was withdrawn from the market in 1995 but recently has been reintroduced. Trials in the United States indicate that the contraceptive efficacy appears to differ with parity. Nulliparous women are reported to have a pregnancy rate of 9% per year, whereas parous women have a pregnancy rate of 20% with perfect use (Table 10.2). A trial comparing the sponge with a vaginal spermicide preparation showed the sponge had a slightly lower pregnancy rate (53).

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Figure 10.5 Copper T380A (ParaGard) intrauterine device.

Intrauterine Contraception

Intrauterine contraceptive devices are very important worldwide but play a minor role in contraception in the United States because of a fear of infection that is no longer justified.

Two IUDs are now in use in the United States: the copper T380A (ParaGard) and the levonorgestrel-releasing T Mirena. The *copper T380A* has bands of copper on the cross arms of the T in addition to copper wire around the stem, providing a total surface area of 380 mm of copper, almost double the surface area of copper of earlier copper devices (Fig. 10.5). It is approved for up to 10 years of continuous use. The *levonorgestrel T* (Fig. 10.6) is approved in the United States for 5 years of use, although studies through 7 years of use show no loss of efficacy (54). **Both provide safe, long-term contraception with effectiveness equivalent**

to tubal sterilization.

Mechanism of Action

Intrauterine devices cause the formation of "biologic foam" within the uterine cavity that contains strands of fibrin, phagocytic cells, and proteolytic enzymes. Copper IUDs continuously release a small amount of the metal, producing an even greater inflammatory response. All IUDs stimulate the formation of prostaglandins within the uterus, consistent with both smooth muscle contraction and inflammation. Scanning electron microscopy studies of the endometrium of women wearing IUDs show alterations in the surface morphology of cells, especially of the microvilli of ciliated cells (55). There

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are major alterations in the composition of proteins within the uterine cavity, and new proteins and proteinase inhibitors are found in washings from the uterus (56). The altered intrauterine environment interferes with sperm passage through the uterus, preventing fertilization. The *levonorgestrel* in the T device is much more potent than natural progesterone. Blood levels of the hormone are about one half those seen with the *levonorgestrel* subdermal implant (*Norplant*) and are sufficient to block ovulation in some women (53). About 85% remain ovulatory. *Levonorgestrel* is thought to produce endometrial atrophy as well as an intrauterine inflammatory response (57).

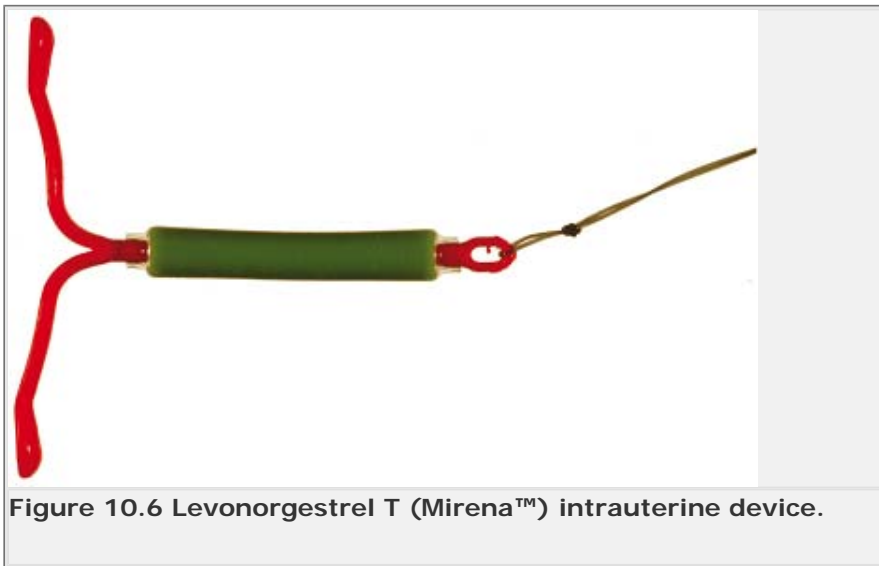


Figure 10.6 Levonorgestrel T (Mirena™) intrauterine device.

The IUD is not an abortifacient. The contraceptive effectiveness does not depend on interference with implantation, although this phenomenon also occurs and is the basis for using copper IUDs for emergency contraception. Sperm can be obtained by laparoscopy in washings from the fallopian tubes of control women at midcycle; fewer sperm are present in the tubal washings from women wearing IUDs (57). Ova flushed from the tubes at tubal sterilization showed no evidence of fertilization in women wearing IUDs (58), and studies of serum β -human chorionic gonadotropin levels in women wearing IUDs do not indicate pregnancy (59).

Effectiveness

The *copper T380A* and the *levonorgestrel T* have remarkably low pregnancy rates, less than 0.2 per 100 woman-years. Total pregnancies over a 7-year period were only 1.1 per 100 for the *levonorgestrel T* and 1.4 for the *copper T380A* (53). Twelve-year data on the *copper T380A* showed a cumulative pregnancy rate of only 1.9 per 100 women (60).

Benefits

Modern IUDs provide excellent contraception without continued effort by the user.

Both the *copper T 380A* and the *levonorgestrel T* protect against ectopic pregnancy.

The *levonorgestrel T*, by releasing *levonorgestrel*, reduces menstrual bleeding and cramping. It has been used extensively to treat heavy menstrual bleeding and is used in Europe and the United Kingdom an alternative to hysterectomy for menorrhagia (61). Additional noncontraceptive benefits include a reduced risk of endometrial cancer (62) and improvement in symptoms of endometriosis (63,64).

Risks

Infection

The Women's Health Study (65) found the *Dalkon Shield* device (now withdrawn from the market) to increase the risk of pelvic inflammatory disease (PID) eightfold when women hospitalized for PID were compared with control women hospitalized for other illnesses. In contrast, risk from the other IUDs was markedly less: Relative risk for PID was 2.2 for the *Progestasert*, 1.9 for the *Copper 7*, 1.3 for the *Saf-T-Coil*, and 1.2 for the *Lippes Loop* (65). Increased risk was detectable only within 4 months of insertion of the IUD. A still larger, prospective World Health Organization study revealed that PID increased only during the first 20 days after insertion. **Thereafter, the rate of diagnosis of PID was about 1.6 cases per 1,000 women per year, the same as in the general population** (66).

Exposure to sexually transmitted pathogens is a more important determinant of PID than is wearing an IUD. In the Women's Health Study, women who were currently married or cohabiting and who said they had only one sexual partner in the past 6 months had no increase in PID (65). In contrast, previously married or single women had marginal increase in risk, even though they had only one partner in the previous 6 months (67). The only pelvic infection that has been unequivocally related to IUD use is actinomycosis (68). It appears that PID with actinomycosis has been reported only in women wearing an IUD.

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Rates of colonization with actinomycosis increase with duration of use for plastic devices but appear to be much less for copper-releasing IUDs.

When PID is suspected in a woman wearing an IUD, appropriate cultures should be obtained, and antibiotic therapy should be administered. Removal of the IUD is not necessary unless symptoms do not improve after 72 hours of treatment (69). Pelvic abscess, if suspected, should be ruled out by ultrasound examination.

Ectopic Pregnancy

If pregnancy occurs in an IUD wearer, it will be ectopic in about 5% of cases. This is because the fallopian tubes are less well protected against pregnancy than is the uterus. Compared with women using no contraception, however, women wearing either the *copper T380A* or the *levonorgestrel T* have an 80% to 90% reduction in the risk of ectopic pregnancy (53), which is a greater reduction than that seen for users of barrier methods. Women using OCs have a 90% reduced risk (69,70). One study reported an increased risk of ectopic pregnancy among past users of older IUDs, but it did not include the current higher-dose copper IUD (*Copper T 380A*) or the *levonorgestrel T* (71).

Fertility

Tubal factor infertility is not increased among nulligravid women who have used copper IUDs, but exposure to sexually transmitted pathogens such as *C. trachomatis* does increase risk (72). The Oxford Study found that women gave birth just as promptly after IUD removal as they did after discontinuing use of the diaphragm (73).

Clinical Management

Contraindications to IUD use listed by the World Health Organization include pregnancy, puerperal sepsis, PID or sexually transmitted diseases current or within the past 3 months, endometrial or cervical cancer, undiagnosed genital bleeding, uterine anomalies, and fibroid tumors that distort the endometrial cavity (69). Infection with HIV is not considered a contraindication for IUD use. No increase in pelvic infection, female-to-male transmission, or viral shedding has been found among HIV-1 infected women. (74,75) Copper allergy and Wilson's disease are contraindications to the use of copper IUDs.

Insertion

At the initial visit, the patient's history is obtained; a physical examination, cervical culture for *Neisseria gonorrhoeae*, and a test for chlamydia are performed; and detailed counseling regarding risks and alternatives is provided. The patient should avoid intercourse until returning for insertion of the device at a second visit. Premedication with oral prostaglandin inhibitors such as *ibuprofen* is strongly advised. Antibiotic prophylaxis has not been found beneficial, probably because the risk of pelvic infection with IUD insertion is so low. A large randomized trial of 1,985 patients receiving either oral *azithromycin* or placebo found no difference in rates of IUD removal during the first 90 days after insertion and no difference in rates of salpingitis (76). These women were screened for STDs only by self-history. The IUD usually is inserted during menses to be sure the patient is not pregnant, but it can be inserted at any time in the cycle if the patient is already using effective contraception (77).

The technique of insertion is as follows:

- **The cervix is exposed with a speculum.** The vaginal vault and cervix are cleansed with a bacteriocidal solution, such as an iodine-containing solution.
- **The uterine cavity should be measured with a uterine sound.** The depth of the cavity should measure at least 6 cm from the external os. A smaller uterus is not likely to tolerate currently available IUDs.

- **A paracervical block** with 10 mL of 1% *lidocaine* mixed with *atropine* (0.5 mg) can be used to avoid vasovagal syncope and minimize discomfort. In some women, serious cardiac arrhythmia, which can occur with cervical stimulation, can be avoided by these measures.
- **Use of a tenaculum for insertion is mandatory to prevent perforation.** The cervix is grasped with a tenaculum and gently pulled downward to straighten the angle between the cervical canal and the uterine cavity. The IUD, previously loaded into its inserter, is then gently introduced through the cervical canal.
- **With the *copper T380A*, the outer sheath of the inserter is withdrawn a short distance**

to release the arms of the T and is then gently pushed inward again to elevate the now-opened T against the fundus. The outer sheath and the inner stylet of the inserter are withdrawn, and the strings are cut to project about 2 cm from the external cervical os.

- **The *Levonorgestrel T* IUD is inserted somewhat differently from the *copper T380A*. The inserter tube is introduced into the uterus until the preset sliding flange on the inserter is 1.5 to 2 cm from the external os of the cervix.** The arms of the T device are then released upward into the uterine cavity, and the inserter is pushed up under them to elevate the IUD up against the uterine fundus.

Intrauterine Devices in Pregnancy

A woman with an IUD in place who has amenorrhea should have a pregnancy test and pelvic examination. If an intrauterine pregnancy is diagnosed and the IUD strings are visible, the IUD should be removed as soon as possible to prevent later septic abortion, premature rupture of the membranes, and premature birth (78). When the strings of the IUD are not visible, an ultrasound examination should be performed to localize the IUD and determine whether expulsion has occurred. **If the IUD is present, there are three options for management:**

- **Therapeutic abortion**
- **Ultrasound-guided intrauterine removal of the IUD**
- **Continuation of the pregnancy with the device left in place**

If the patient wishes to continue the pregnancy, ultrasound evaluation of the location of the IUD is advised (79). If the IUD is not in a fundal location, ultrasound-guided removal using small alligator forceps is advised. If the location is fundal, the IUD should be left in place. When pregnancy continues with an IUD in place, the patient must be warned of the symptoms of intrauterine infection and should be cautioned to seek care promptly for fever or flulike symptoms, abdominal cramping, or bleeding. At the earliest sign of infection, high-dose intravenous antibiotic therapy should be given and the pregnancy evacuated promptly.

Duration of Use

Annual rates of pregnancy, expulsions, and medical removals decrease with each year of use (80,81). Therefore, a woman who has had no problem by year 5, for example, is very unlikely to experience problems in the subsequent years. The *Copper T380A* is approved for 10 years and the *levonorgestrel T* for 5 years. Actinomyces can be detected by cervical cytology. Should actinomyces-like particles be found, removal of the IUD and treatment with oral penicillin is recommended.

Choice of Devices

Both of the IUDs available in the United States, the *Copper T380A* and the *Levonorgestrel T*, provide protection for many years, have remarkably low pregnancy rates, and reduce the risk

of ectopic pregnancy substantially. The *levonorgestrel T* reduces the amount of menstrual bleeding and dysmenorrhea. The *copper T380A* can be expected to increase menstrual bleeding. It is also the most effective means for emergency contraception.

Hormonal Contraception

Hormonal contraceptives are female sex steroids, synthetic estrogen and synthetic progestin (progestin), or progestin only. They can be administered in the form of OCs, patches, implants, and injectables. The most widely used hormonal contraceptive is the combination OC. Combination OCs can be monophasic, with the same dose of estrogen and progestin administered each day, or multiphasic, in which varying doses of steroids are given through a 21-day cycle. Typically, they are administered for 21 days beginning on the Sunday after a menstrual period, then discontinued for 7 days to allow for withdrawal bleeding that mimics the normal menstrual cycle. Alternatively, OCs can be started on the first day of menstruation. The 28-day version provides placebo tablets for the last 7 days of the cycle so the user simply takes one pill a day and starts a new pack as soon as the first pack is completed. Progestin-only formulations contain no estrogen. These are taken every day without interruption. Other forms of hormonal contraception include transdermal administration with the patch, injectable progestins and estrogen-progestin combinations, subdermal implants that release progestin, and the vaginal rings that release either estrogen-progestin or progestin alone (82).

Steroid Hormone Action

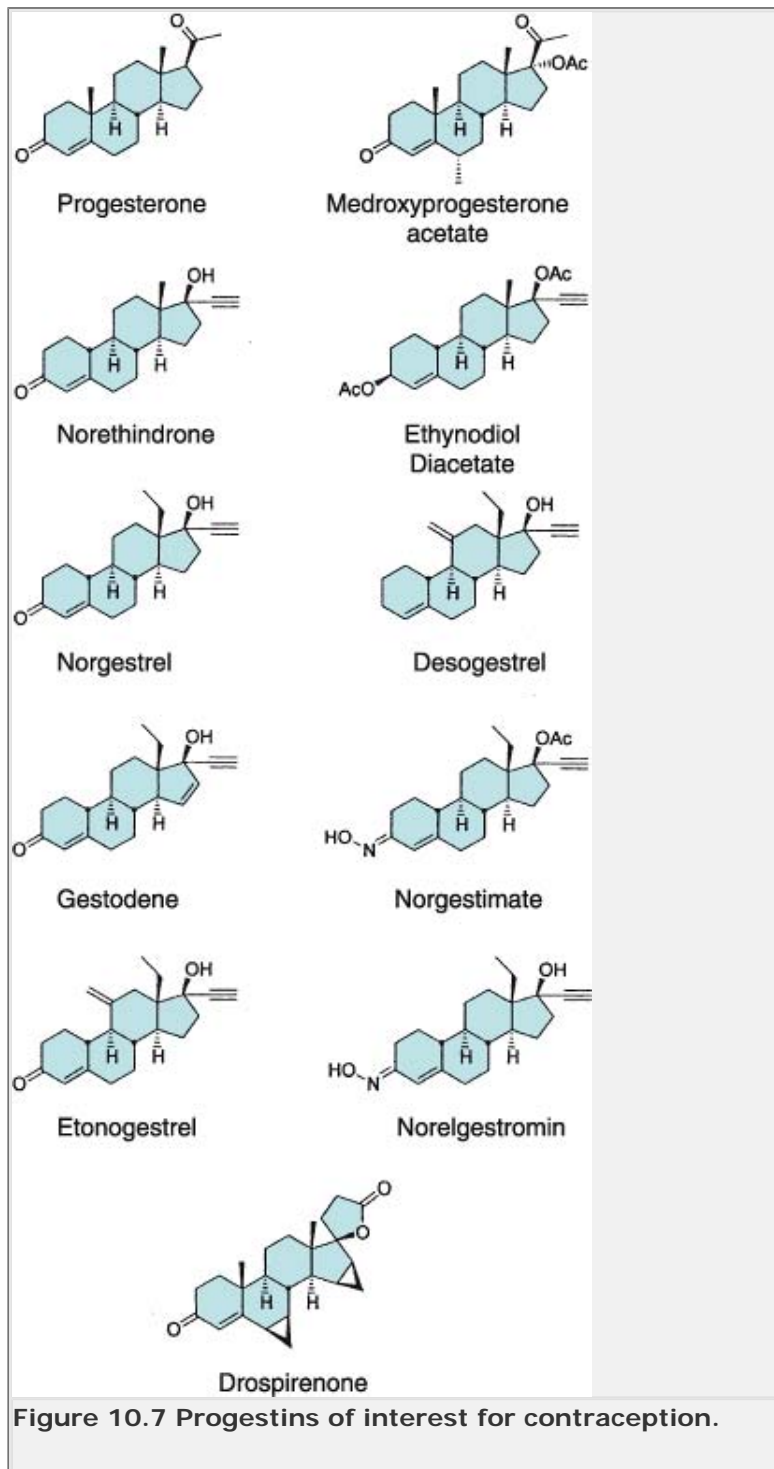
Sex steroids were originally defined by their biologic activity. They are characterized by their affinity for specific estrogen, progesterone, or androgen receptors, as well as by their biologic effects in different systems (83). Steroids are rapidly absorbed in the gut but go directly into the liver through the portal circulation, where they are rapidly metabolized and inactivated. Therefore, large doses of steroids are required when they are administered orally. The addition of the ethinyl group to carbon-17 of the steroid molecule hinders degradation by the liver enzyme 17-hydroxysteroid dehydrogenase.

Progestins

Progestins are synthetic compounds that mimic the effect of natural progesterone but differ from it structurally (Fig. 10.7). The progestins differ from each other in their affinities for estrogen, androgen, and progesterone receptors; their ability to inhibit ovulation; and their ability to substitute for progesterone and antagonize estrogen. Some are directly bound to the receptor (*levonorgestrel*, *norethindrone*), whereas others require bioactivation as, for example, *desogestrel*, which is converted in the body to its active metabolite, *etonogestrel*. The 17-acetoxy progestins (e.g., *medroxyprogesterone acetate*) are bound by the progesterone receptor. *Norgestrel* exists as two stereoisomers, identified as *dextronorgestrel* and *levonorgestrel*. Only *levonorgestrel* is biologically active. Three newer progestins (*norgestimate*, *desogestrel*, and *gestodene*) are viewed as more "selective" than the other 19-nor progestins, in that they have little or no androgenic effect at doses that inhibit ovulation (84). The FDA has approved *norgestimate*- and *desogestrel*-containing OCs, and *gestodene* is available in Europe. *Gestodene* is a derivative of

levonorgestrel that is more potent than the other preparations (i.e., very little of it is required for antifertility effects). Similarly, *norelgestromin* is an active metabolite of *norgestimate* and more potent than the parent compound. It is used in the transdermal patch. *Drospirenone*, a novel progestin recently introduced in the United States, is a derivative of the diuretic spironolactone. It has high affinity for progesterone receptors, mineralocorticoid

receptors, and androgen receptors. It acts as a progesterone agonist but is a mineralocorticoid antagonist and androgen antagonist (85). Comparative studies suggest a small decrease in body weight and in blood pressure, with equivalent cycle control and contraceptive efficacy, in women taking an OC containing 3 mg of *drospirenone*/30 μ g *ethinyl estradiol* versus women taking a 150 μ g *levonorgestrel*/30 μ g *ethinyl estradiol* preparation (86). Pilot studies of women with polycystic ovary syndrome have shown good cycle control and reduction in androgen levels with no change in weight, blood pressure, or glucose metabolism (87). There are no studies published to date that compare the effects of *drospirenone* OC with conventional OCs in these patients.



Estrogens

In the United States, OCs contain either one of two estrogens: *mestranol* or *ethinyl estradiol (EE)*. *Mestranol* is *EE* with an extra methyl group. It requires bioactivation in the liver, where the methyl group is cleaved, releasing the active agent, *EE*. Oral contraceptives with

35 µg of *EE* provide the same blood levels of hormone as do OCs containing 50 µg of *mestranol* (88).

Antifertility Effects

Combination Estrogen Progestin Contraceptives

Ovulation can be inhibited by estrogen or by progestin alone. Pharmacologic synergism is exhibited when the two hormones are combined and ovulation is suppressed at a much lower dose of each agent. Combination OCs, patches, and the *NuvaRing* suppress basal follicle-stimulating hormone FSH and LH. They diminish the ability of the pituitary gland to synthesize gonadotropins when it is stimulated by the hypothalamic GnRH (89). Ovarian follicles do not mature, little estradiol is produced, and there is no midcycle LH surge. Ovulation does not occur, the corpus luteum does not form, and progesterone is not produced. This blockade of ovulation is dose related. Newer low-dose OCs do not provide as dense a block and allow somewhat higher baseline FSH and LH levels than higher dose formulations (90). This makes ovulation somewhat more likely to occur if pills are missed or if the patient takes another medication that reduces blood levels of the contraceptive steroids.

Progestin-only Preparations

The mode of action of progestin-only contraceptives is highly dependent on the dose of the compound (91). With low levels of progestin in the blood, ovulation will occur part of the time. With the progestin-only "minipill," which supplies 0.3 mg of *norethindrone* per day (*Micronor*), 40% of cycles are ovulatory, 25% have inadequate luteal function, 18% have follicular maturation without ovulation, and 18% have complete suppression of follicle development. At moderate levels of progestin in the blood, normal basal levels of FSH and LH are present, and some follicle maturation may occur. Estradiol production is present, and the surge of estradiol that would normally trigger pituitary release of LH occurs; there is no answering LH surge, however, and hence ovulation does not occur. At higher levels of progestin in the blood, the amount of basal FSH is reduced, and there is less follicular activity, less estradiol production, and no LH surge.

Transdermal Hormonal Contraception

The patch (*OrthoEvra*), which is affixed to the user's skin, and the vaginal *NuvaRing* both contain combinations of *EE* and a potent progestin. Both provide sustained release of the steroids and result in relatively constant serum levels that are less than peak levels seen with OCs but sufficient to prevent ovulation.

Hormonal Implants

With the subdermal implant that releases *levonorgestrel* there is some follicular maturation and estrogen production, but LH peak levels are low and ovulation is often inhibited. In the first year of use, ovulation is believed to occur in about 20% of cycles. The proportion of ovulatory cycles increases with time, probably as a result of the decline in hormone release. By the fourth year of use, 41% of cycles are ovulatory. The more potent progestin released by the *etonogestrel* implant is even more effective at preventing ovulation (92). The mechanisms of action of low-dose progestins are believed to include effects on the cervical mucus, endometrium, and tubal motility. The scant, dry cervical mucus that occurs in women using

these preparations inhibits sperm migration into the upper tract. Progestins decrease nuclear estrogen receptor levels, decrease progesterone receptors, and induce activity of the enzyme 17-hydroxysteroid dehydrogenase, which metabolizes natural estradiol 17β (92).

The sustained release offered by contraceptive implants allows for highly effective contraception at relatively low blood levels of the steroid. Figure 10.8 depicts expected

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steroid blood levels with implants, injectables, and oral contraceptives. An additional mechanism for contraception has been discovered with the antiprogestone *mifepristone (RU486)*. In the normal cycle, there is a small amount of progesterone production from the follicle just before ovulation. This progesterone appears essential to ovulation, because if the antiprogestone is given before ovulation, this can be delayed for several days (93,94).

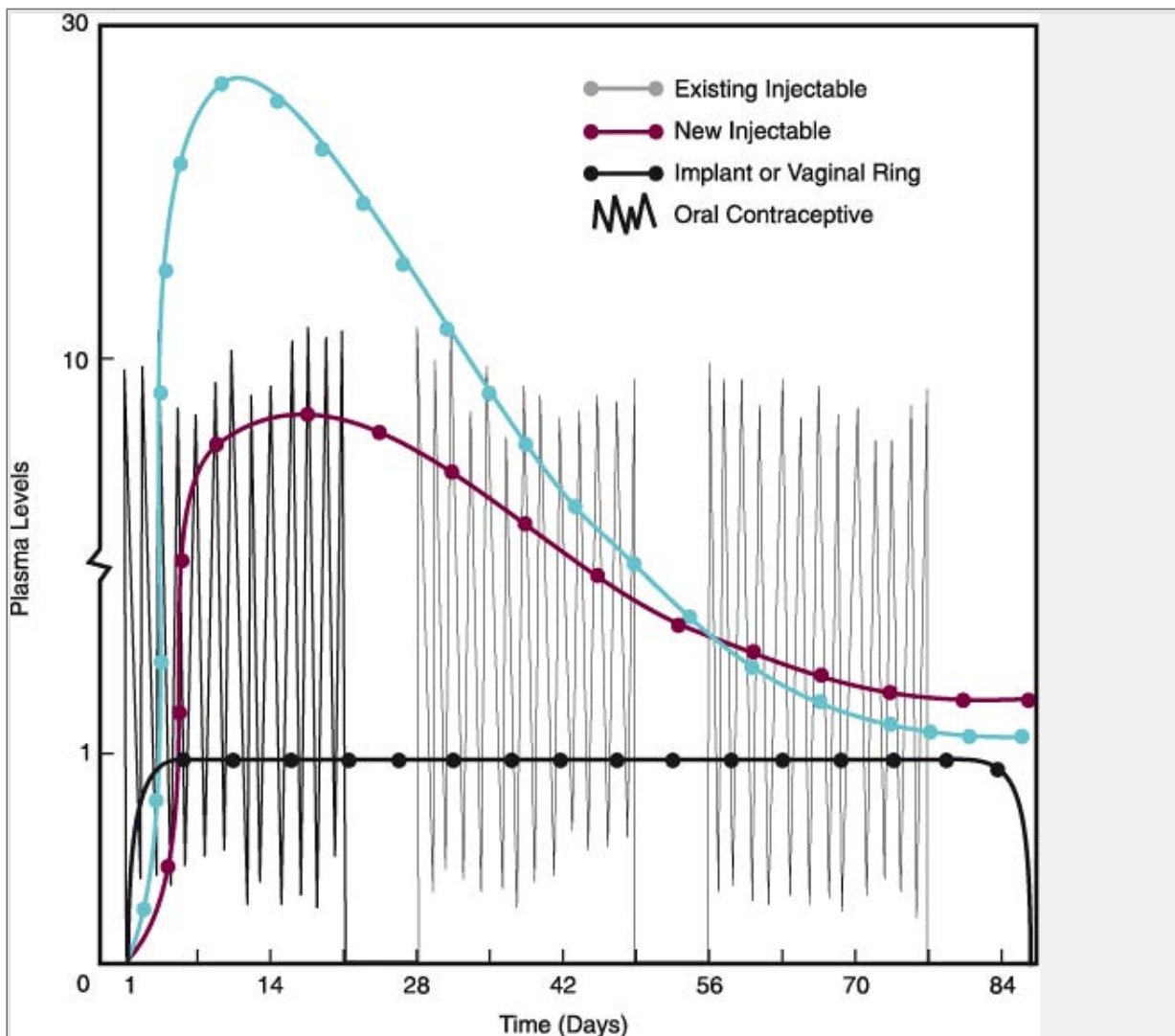


Figure 10.8 Schematic representation of the expected pharmacokinetic profiles of progestogens administered in different formulations. (From Landgren BM. Mechanism of action of gestagens. *Int J Gynaecol Obstet* 1990;32:95–110, with permission.)

Efficacy of Hormonal Contraception

When used consistently, combination OCs have pregnancy rates as low as 2 to 3 per 1,000 women per year. Progestin-only OCs are less effective than combination estrogen-progestin preparations, with best results of 3 to 4 pregnancies per 100 woman-years. All

methods have the potential for user error; therefore, there may be a 10-fold difference between the best results and results in typical users of OCs. Injectable progestins and implants are much less subject to user error than are OCs. The difference between the best results and results in typical users is small and is comparable to pregnancy rates after tubal sterilization (Table 10.2). Pregnancy rates with the *OrthoEvra* patch (95) and the *NuvaRing* (96) were equivalent to those of OCs in studies published to date; however, because it is easier to use these methods consistently, larger studies may well demonstrate better typical user results than with OCs.

Metabolic Effects and Safety

Venous Thrombosis

Older studies linked OC use to venous thrombosis and embolism, cerebral vascular accidents, and heart attack (97,98). More recent studies have found a much lower risk (99). A reevaluation of the older literature on venous thrombosis reveals that absolute risk was strongly determined by other very obvious predisposing causes of thrombosis that are now considered contraindications to OC use: previous thrombosis, preexisting vascular disease, coronary artery disease, leukemia, cancer, and serious trauma (100).

Normally, the coagulation system maintains a dynamic balance of procoagulant and anticoagulant systems in the blood. Estrogens affect both systems in a dose-related fashion. For most women, fibrinolysis (anticoagulation) is increased as much as coagulation, maintaining the dynamic balance at increased levels of production and destruction of fibrinogen (101,102) (Fig.10.9). Current low-dose OCs have less measurable effect on the coagulation system, and fibrinolytic factors increase at the same rate as procoagulant factors (103,104). Lower estrogen dose (30 to 35 µg *EE*) reduces the risk of a thromboembolic event when compared with higher dose (50 µg estrogen) OCs (105) (Table 10.5). Theoretically, thrombosis risk should be even lower with current OCs containing only 20 µg of *EE*, but this finding has not been demonstrated.

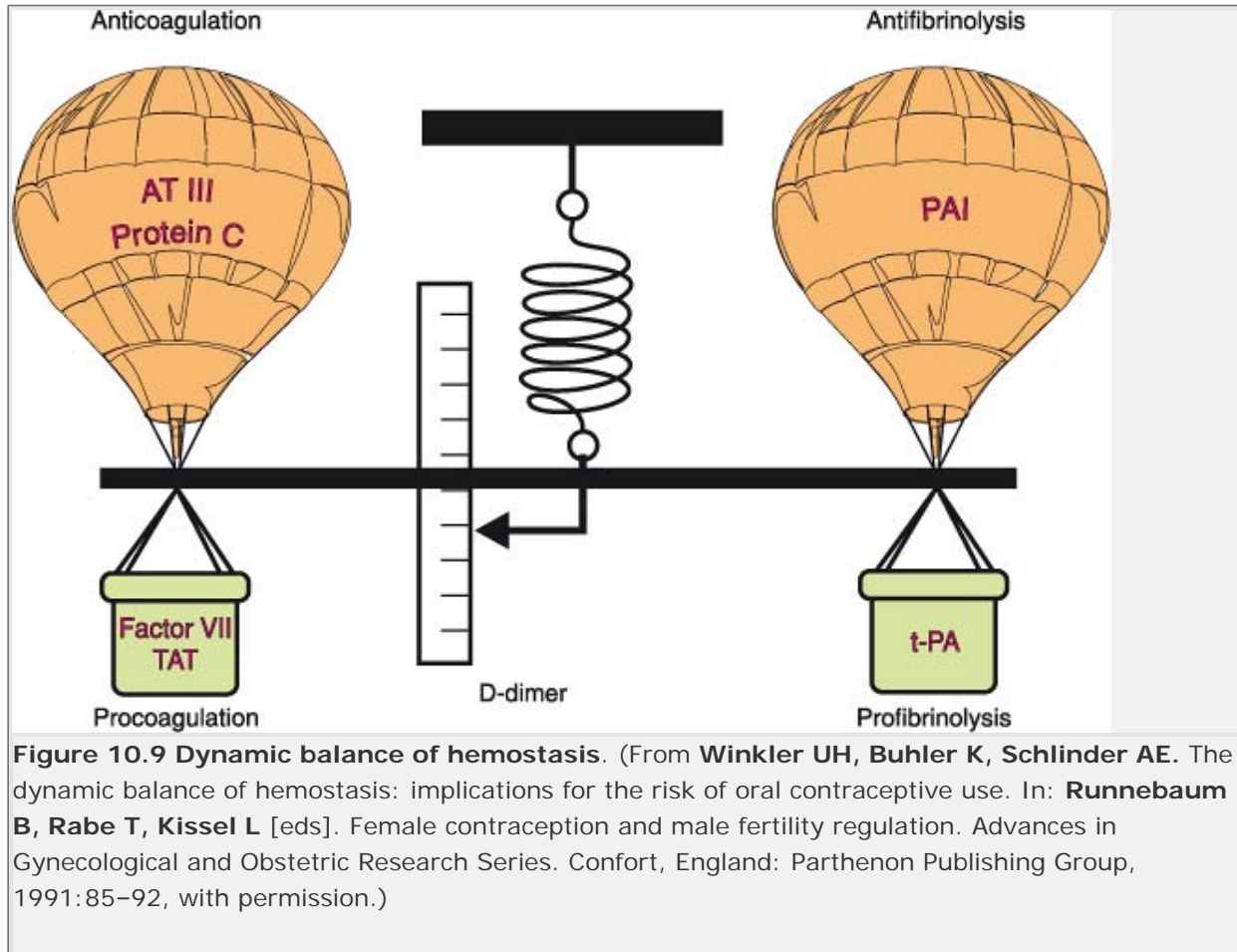
The absolute risk of thrombosis in OC users taking pills containing 30 to 35 µg *EE* is 3 per 10,000 per year, compared with 1 per 10,000 reproductive-aged women not using OCs and 6 per 10,000 in pregnancy (106). Thrombosis risk is apparent by 4 months after starting estrogen-containing OCs and does not increase further with continued use. Risk is highest during the first year of use (107).

Thrombophilia

Changes in the coagulation system are detectable in all women, including those taking lower-dose OCs; however, some women are genetically predisposed to

thrombosis when challenged by pregnancy or administration of exogenous estrogen. In one study, hemostatic variables in women given low-dose OCs who had previous thrombosis with OCs were compared with women with no thrombosis (108). Women known to have inherited thrombophilic disorders were excluded. Both groups of women had significant changes in clotting factors: increased factor VII, factor VIII, and protein C; and decreased antithrombin, activated protein C sensitivity ratio, and protein S. However, the women with a history of thrombosis who were taking OCs had more pronounced changes. They were "high hemostatic responders" when exposed to OCs. **Women with inherited deficiencies of antithrombin III, protein C, or protein S are at very high risk for thrombosis with pregnancy or estrogen therapy, but they make up a very small proportion of potential OC users. A much more common variation, factor V Leiden, has been**

identified. This genetic variation exists in 3% to 5% of the white population. It codes for a one amino acid mutation in the factor V protein, inhibiting cleavage of the protein by activated protein C, which is an essential step in maintaining the balance between coagulation and fibrinolysis (109). **Risk for a first thromboembolic episode among women using OCs was 2.2 per 10,000 woman-years for women without the factor V mutation and 27.7 per 10,000 woman-years for women with the mutation** (110). Cigarette smoking did not affect this risk. There are pronounced ethnic differences in the presence of this mutation. The Leiden allele is found in 3% to 5% of whites but is rare in Africans, Asians, Amerindians, Eskimos, and Polynesians (111). A similar mutation is found in the prothrombin gene at position 20210 and is described as prothrombin G20210A. It is found in 3% of the European population and is also strongly associated with venous thrombosis in women taking OCs (112).



Estrogen (Dose)	(Rate/10,000 Person Years)	Relative Risk (All Cases)	Relative Risk (Proven Diagnosis)
<50 µg	4.2	1.0	1.0 ^a
50 µg	7.0	1.5	2.0 (0.0–4.0)
>50 µg	10.0	1.7	3.2 (2.4–4.3)

^a Baseline risk used to calculate risk for higher doses.

From Gerstman BB, Piper JM, Tomita DK, et al. Oral contraceptive dose and the risk of deep venous thrombosis. *Am J Epidemiol* 1991;133:32–37, with permission.

Pregnancy is an even greater challenge for women with inherited defects of anticoagulation (113).

A woman who sustains a venous event while using OCs should be evaluated thoroughly after she has recovered. Assessment should include measurement of antithrombin III, protein C, and protein S levels; resistance to activated protein C, serum homocysteine, factor V Leiden mutation, and the prothrombin G20210A mutation; and testing for antiphospholipid antibody. It should not be assumed that hormonal contraception was the unique cause of the thrombotic episode.

In a study of routine screening for factor V Leiden, the authors concluded that routine screening of patients before hormonal contraception is taken is not justified because effective contraception would be denied to 5% of white women, and only a small number of fatal pulmonary emboli would be prevented (114).

Furthermore, if pregnant women were screened and those who screened positive were then treated with heparin, the number of cases of fatal bleeding might equal or exceed the number of fatal pulmonary emboli. However, screening women with a personal or family history of deep vein thrombosis before starting estrogen-containing hormonal contraception or pregnancy is strongly recommended.

Thrombosis and the New Progestins

Several studies have found a modest increased risk of venous thrombosis when users of OCs containing the newer progestins *desogestrel*

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or *gestodene* combined with 20 to 30 µg of *EE* were compared with users of *levonorgestrel* combined with the same doses of estrogen (115). A great controversy ensued, which continues to this day. Some have concluded that the biases "attrition of susceptibles," "adverse selection," and "healthy user bias" explain the apparent increase in thrombosis. Most cases of venous thrombosis attributable to OCs occur during the initial months of use (116). Hence, comparing new users to women already taking OCs for some time without incident will demonstrate an apparent increase with the new product that is artificial. Also, physicians may presume that newer drugs are safer and prescribe them selectively for women with risk factors. Analysis of data from a large European study of women who experienced thrombosis with different OCs has shown that the apparent risk of thrombosis was lowest with the first low-dose pills introduced and highest with those recently introduced, even though the newest pill had the lowest estrogen dose (115) (Fig. 10.10). In contrast, **two large meta-analyses of the available studies have concluded that there may be a low level of increased risk for venous thrombosis and embolism (VTE) in users of OCs containing *desogestrel* or *gestodene*** (117,118). A relative risk of 1.7 was found in both analyses. The absolute risk of VTE in young women was estimated as 1.5 per 10,000 with OCs containing *EE/levonorgestrel* and 2.6 per 10,000 with OCs containing *EE* and either *desogestrel* or *gestodene*. Because the absolute risk is still very small, the issue cannot be unequivocally resolved with observational data (117).

Ischemic Heart Disease

Ischemic heart disease and stroke were the major causes of death attributed to OC use in the past. It is now known that the principal determinants of risk are advancing age and cigarette smoking (119). With the higher-dose OCs used in the 1980s, smoking had a profound effect on risk. Women smoking 25 or more cigarettes per

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day had a 30-fold increased risk for myocardial infarction if they used OCs, compared with nonsmokers not using OCs (120) (Fig. 10.11). Use of OCs is now much safer because

most women are taking low-dose pills and because physicians prescribe selectively, excluding women with major cardiovascular risk factors. A very large study in the United States confirms the safety of OCs as currently prescribed. A total of 187 women aged 15 to 44 years with confirmed myocardial infarction were identified during 3.6 million woman-years of observation in the Kaiser Permanente Medical Care Program in California from 1991 to 1994. This is a rate of 3.2 per 100,000 woman-years (121). Nearly all of the current users took OCs with less than 50 µg of *EE*. **After adjusting for age, illness, smoking, ethnicity, and body mass index, risk for myocardial infarction was not increased by OC use (OR, 1.14; CI 95%, 0.27 to 4.72). Of heart attack victims, 61% smoked; only 7.7% were current users of OCs.** In a later study, the same investigators pooled results from the California study with a similar study from Washington State. The results were the same. **Current users of low-dose OCs had no increased risk for myocardial infarction after adjustment for major risk factors and sociodemographic factors** (122). Past use of OCs does not increase risk for subsequent myocardial infarction (123).

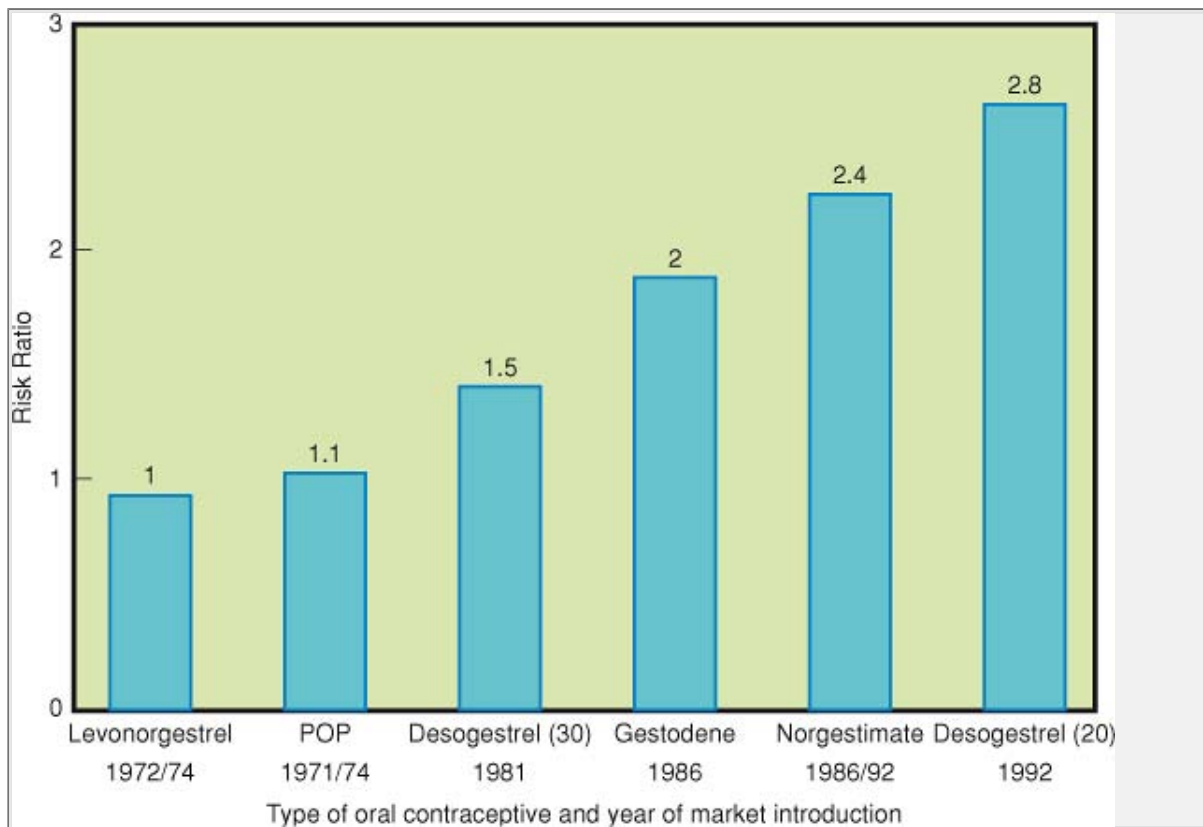


Figure 10.10 Risk ratios of oral contraceptives for thrombosis by year of market introduction for women aged 25 to 44 years. LNG, levonorgestrel with 30 µg ethinyl estradiol; POP, progesterone-only pills; GES, gestodene with 30 µg ethinyl estradiol; NORG, norgestimate with 35 µg of ethinyl estradiol; DES20, desogestrel with 20 µg of ethinyl estradiol. (From **Lewis MA, Heinemann LAJ, MacRae KD, et al.** The increased risk of venous thrombosis and the use of third generation progestagens: role of bias in observational research. *Contraception* 1996;54:5-13, with permission.)

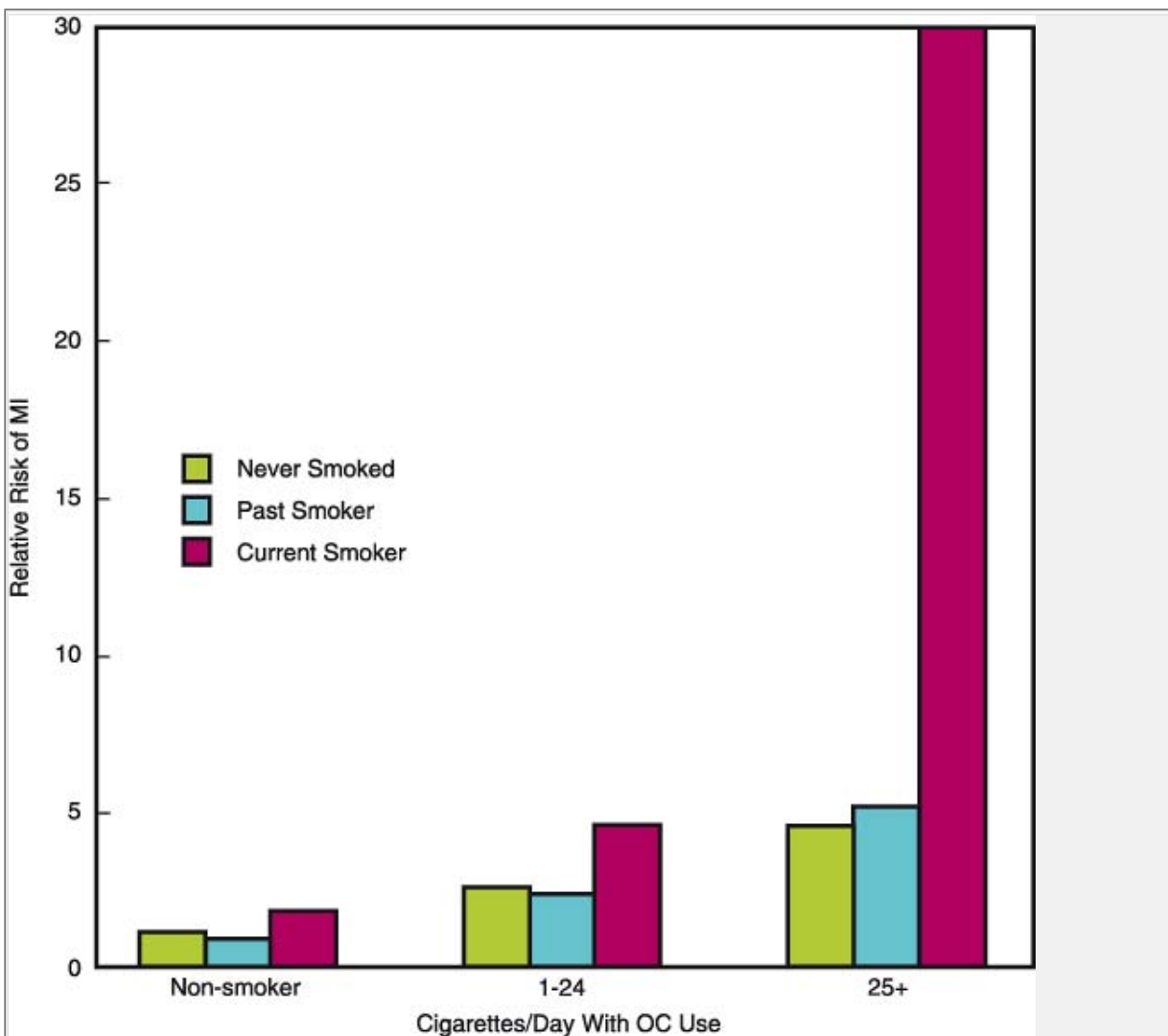


Figure 10.11 Risk for myocardial infarction (MI) in women younger than 50 years of age: effect of oral contraceptives (OC) and smoking. (From Rosenberg L, Kaufman DW, Helmrich SP, et al. Myocardial infarction and cigarette smoking in women younger than 50 years of age. *JAMA* 1985;253:2965–2969, with permission.)

One of the larger studies of so-called third-generation OCs found that OCs containing the new progestins *desogestrel* or *gestodene* are less likely to be associated with myocardial

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infarction than OCs with similar estrogen doses and levonorgestrel (124). Myocardial infarction risk was strongly increased among smokers, even after adjustment for OC use, but smokers who used OCs with the new progestins were less likely to have myocardial infarction than smokers who used the older OCs (124,125). These findings are biologically plausible based on the beneficial effect on lipids of OCs containing the new progestins.

Oral Contraceptives and Stroke

In the 1970s, OC use appeared to be linked to risk of both hemorrhagic and thrombotic stroke, but these studies failed to take into consideration preexisting risk factors (126). **Although a rare form of cerebrovascular insufficiency, moyamoya disease, is clearly linked to OC use (127), new information shows no risk for women who are otherwise healthy and who use currently available low-dose pills.** One study identified all Kaiser Permanente Medical Care Program patients aged 15 to 44 years who sustained fatal or nonfatal stroke in California from 1991 to 1994 (128). **Hypertension, diabetes, obesity, current**

cigarette smoking, and black race were strongly associated with stroke risk, but neither current nor past OC use was associated with stroke in this study. A World Health Organization (WHO) study of cases from 1989 to 1993 from 17 countries in Europe and the developing world included women taking higher-dose OCs as well as low-dose OCs. European women using low-dose OCs had no increased risk for either type of stroke, thrombotic or hemorrhagic. Those taking higher-dose OCs did have measurable risk (129,130). Women in developing countries had an apparent modest increase in risk, but this finding was attributed to undetected existing risk factors. Another study from Europe found less stroke risk from low-dose pills than from older, higher-dose pills, and that risk was less if the patient's blood pressure was checked before starting OCs. The authors concluded that a small risk from low-dose OCs could be controlled if women with hypertension were not given OCs (131).

Women who smoke and those who have hypertension and diabetes are clearly at increased risk for cardiovascular disease regardless of whether they use oral contraceptives. The important question is whether risk is further increased if they use low-dose OCs, and if so, by how much. The World Health Organization study described previously provides some insight: **Smokers taking OCs had seven times the risk of ischemic (thrombotic) stroke when compared with smokers who did not use OCs, and hypertensive women had 10-fold increased risk if they took OCs, but a fivefold risk if they did not** (129). Similarly, a study from Denmark found that women with diabetes had a fivefold increase risk for stroke, which increased to 10-fold if they took OCs (132). Unfortunately, these data were not limited to low-estrogen OCs. The data suggest that although risk is primarily determined by the predisposing condition—hypertension, diabetes, or cigarette smoking—the risk can be magnified by OC use, even when the OCs are low dose. The current practice in the United States of limiting OC use by women older than 35 years of age to nonsmokers without other vascular disease risk factors is prudent.

Blood Pressure

Oral contraceptives have a dose-related effect on blood pressure. With the older high-dose pills, as many as 5% of patients could be expected to have blood pressure levels greater than 140/90 mm Hg. The mechanism is believed to be an estrogen-induced increase in renin substrate in susceptible individuals. **Current low-dose pills have minimal blood pressure effects, but surveillance of blood pressure is advised to detect the occasional idiosyncratic response.**

Glucose Metabolism

Oral estrogen alone has no adverse effect on glucose metabolism, but progestins exhibit insulin antagonism (133). Older OC formulations with higher doses of progestins produced abnormal glucose tolerance tests with elevated insulin levels in the average patient. The effect on glucose metabolism, similar to the effect on lipids, is related to androgenic potency of the progestin and to its dose.

Lipid Metabolism

Higher-dose OCs could have significant adverse effects on lipids (134). Androgens and estrogens have competing effects on hepatic lipase, a liver enzyme

critical to lipid metabolism. Estrogens depress low-density lipoproteins (LDL) and elevate high-density lipoproteins (HDL), changes that can be expected to reduce the risk of atherosclerosis (135). Androgens and androgenic progestins can antagonize these beneficial changes, reducing HDL and elevating LDL levels. Estrogens elevate triglyceride levels. Low-dose formulations have minimal adverse effect on lipids (136), and the newer

formulations (with *desogestrel* and *norgestimate* as the progestin) produce potentially beneficial changes by elevating HDL and lowering LDL (137). Although average values of a large group show only small lipid changes with the use of current OCs, an occasional patient may have exaggerated effects. Women whose lipid values are higher than the mean before treatment are more likely to experience abnormalities during treatment (136).

Other Metabolic Effects

Oral contraceptives can produce changes in a broad variety of proteins synthesized by the liver. The estrogen in OCs increases circulating thyroid-binding globulin, thereby affecting tests of thyroid function that are based on binding, increasing total thyroxine (T_4) levels, and decreasing triiodothyronine (T_3) resin uptake. The results of actual thyroid function tests, as measured by free T_4 and radioiodine tests, are normal (138).

Oral Contraceptives and Neoplasia

Endometrial Cancer and Ovarian Cancer

Combination OCs reduce the risk of subsequent endometrial cancer and ovarian cancer (139,140). Two-year use of OCs reduces the risk of endometrial cancer by 40%, and 4 or more years of use reduces the risk by 60%. Another study found a 50% reduction in ovarian cancer risk for women who took OCs for 3 to 4 years and an 80% reduction with 10 or more years of use (141). There was some benefit from as little as 3 to 11 months of use. Benefit continues for at least 15 years from last use (125,127,142). National vital statistics data from England support these observations. In England and Wales, ovarian cancer mortality is declining in women younger than 55 years of age, and this decline has been attributed to OC use (143). Low-dose pills provide protection equivalent to older, higher-dose OCs (144). A similar reduction of risk of ovarian epithelial cancer has been found in a prospective study from Norway and Sweden, with borderline tumor risk equally reduced. Progestin-only contraceptives provided risk reduction equivalent to that of combined OCs (145).

Cervical Cancer

There may be a weak association between OC use and squamous cancer of the cervix. A systematic review of 28 epidemiologic studies of cervical cancer in OC users compared with those who never used OCs reported summary relative risks of 1.1 (95% CI 1.1–1.2) at less than 5 years of pill use, 1.6 (1.4–1.7) at 5 to 9 years, and 2.2 (1.9–2.4) at 10 or more years (146). A critique of this study argued that causation is not proved because few of the studies cited adequately control for the key behavioral factors of partners, use of barrier contraception, and adequacy of cervical cancer screening (147). Important risk factors are early sexual intercourse and exposure to HPV. Women who have used OCs typically started sexual relations at younger ages than women who have not used OCs and, in some studies, report having had more partners. These factors also increase one's chance of acquiring HPV, the most important risk factor for cervical cancer. Because barrier contraceptives reduce the risk of cervical cancer, use of alternative choices for contraception can compound the difficulty in establishing an association with OC use alone (148). The presence of HPV types 16 or 18 is associated with a 50-fold increase in risk for preneoplastic lesions of the cervix (149). Adenocarcinomas of the cervix are rare, but they are not as easily detected as other lesions by screening cervical cytology, and the incidence appears to be increasing. One study found a doubling of risk for adenocarcinoma with OC use that increased with duration of use, reaching a relative risk of 4.4 if total use of OCs exceeded 12 years (150). The results of this study were adjusted for history

of genital warts, number of sexual partners, and age at first intercourse. Because adenocarcinoma of the cervix is rare, absolute risk is low. If this apparent association is real, the cumulative risk of long-term OC use to 55 years of age would be about 1 in 1,000 patients (151).

Use of OCs is, at most, a minor factor in causation of cervical cancer; however, these findings emphasize the need to provide cervical cancer screening as part of contraceptive services. To reduce risk, women who are not in mutually monogamous relationships should be advised to use barrier methods in addition to hormonal contraception.

Breast Cancer

There is a large volume of conflicting literature on the relationship between OC use and breast cancer (152). Generally, no increase in overall risk is found from OC use, but some studies have found that risk may increase in women who used OCs before their first term pregnancy, used OCs for many years, are nulligravid, are young at the time of diagnosis, or continue using OCs in their 40s. A meta-analysis of 54 studies of breast cancer and hormonal contraceptive use reanalyzed data on 53,297 women with breast cancer and 100,239 controls from 25 countries, representing about 90% of the epidemiologic data available worldwide at that time (153). Current use of OCs was associated with a very small but statistically stable 24% increased risk (RR, 1.24; 95% CI, 1.15–1.33). The risk fell rapidly after discontinuation, to 16% 1 to 4 years after stopping and to 7% 5 to 9 years after stopping. Risk disappeared 10 years after cessation (RR, 1.01; 95% CI, 0.96–1.05). Results did not differ in any important way by ethnic group, reproductive history, or family history. Since the meta-analysis was published, subsequent studies have found no increased risk. A case control study of 4,575 women with breast cancer and 4,682 controls aged 35 to 64 years living in five cities in the United States concluded that **breast cancer risk was not increased for current or past users of OCs and did not increase with prolonged or with higher-estrogen OC use** (154). **Neither family history of breast cancer nor beginning use at a young age was associated with increased risk. A similar study in Sweden compared 3,016 women aged 50 to 74 years who had invasive breast cancer with 3,263 controls of the same age. No relation was found between past use of OCs and breast cancer** (155).

The controversy over the association between breast cancer and OC use is likely to continue. For the present, however, the best information available is reassuring that there is little or no connection.

Liver Tumors

Oral contraceptives have been implicated as a cause of benign adenomas of the liver. These hormonally responsive tumors can cause fatal hemorrhage. They usually regress when OC use is discontinued; risk is related to prolonged use (156). There is a strong correlation between OC use and hepatocellular adenoma. Fortunately, the tumors are rare; about 30 cases per 1,000,000 users per year have been predicted with older formulations. Presumably, newer low-dose products pose less risk. A link to hepatic carcinoma has been proposed. This cancer is closely associated with chronic hepatitis B and C infections and is usually seen in cirrhotic livers. There are case reports of hepatocellular carcinoma in young women with no risk factors other than long-term OC use (157). However, a large study from six countries in Europe found no association between use of OCs and subsequent liver cancer (158).

Health Benefits of Oral Contraceptives

Oral contraceptives have important health benefits (Table 10.6). **These include contraceptive and noncontraceptive benefits** (159).

Contraceptive Benefits

Oral contraceptives provide highly effective contraception, preventing unwanted pregnancy, an important public health problem. Where safe abortion services are not available, women seek unsafe services and risk death from septic abortion. Combination OCs block ovulation and offer marked protection from ectopic pregnancy. Risk of ectopic pregnancy in a woman taking combination OCs is estimated to be 1/500 of the risk of women not using contraception; however, progestin-only OCs appear to increase risk of ectopic pregnancy (160).

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Table 10.6 Established and Emerging Noncontraceptive Benefits of Oral Contraceptives	
<i>Established Benefits</i>	
Menses-related	
Increased menstrual cycle regularity	
Reduced blood loss	
Reduced iron-deficiency anemia	
Reduced dysmenorrhea	
Inhibition of ovulation	
Fewer ovarian cysts	
Fewer ectopic pregnancies	
Other	
Reduced fibroadenomas/fibrocystic breast changes	
Reduced acute pelvic inflammatory disease	
Reduced endometrial cancer	
Reduced ovarian cancer	
Emerging Benefits	
Increased bone mass	
Reduced acne	
Reduced colo-rectal cancer	
Reduced uterine leiomyomata	
Reduced rheumatoid arthritis	
Treatment of bleeding disorders	
Treatment of hyperandrogenic anovulation	
Treatment of endometriosis	
Treatment of perimenopausal changes	
From Burkman, R, Schlesselman, JJ, Zieman, M. Safety concerns and health benefits associated with oral contraception. <i>Am J Obstet Gynecol</i> 2004; 190(suppl):S12.	

Noncontraceptive Benefits

As noted earlier, **OC use produces strong and lasting reduced risk for endometrial and ovarian cancer.** In addition, protection has been found for women with known hereditary ovarian cancer. **Any past use of OCs conferred a 50% reduction in ovarian cancer risk when women with this history who took OCs were compared with their sisters as controls (OR, 0.5; 95% CI, 0.3–0.8). Protection increased with increasing duration of use** (161). The mechanism of action of OCs in the prevention of ovarian cancer is unknown but may involve selective induction of apoptosis (programmed cell death). Macaques treated with *EE* plus *levonorgestrel* or *levonorgestrel* alone showed an increase in the proportion of ovarian epithelial cells in apoptosis in comparison with animals fed a diet containing no hormones (162).

Chlamydial colonization of the cervix appears more likely in OC users than in nonusers but, despite this finding, several case control studies have found a reduced risk of acute pelvic inflammatory disease among OC users (163,164). In contrast, a recent study found no protection with OC use (165).

Other documented benefits of OC use include a significant reduction in the need for biopsies for benign breast disease and surgery for ovarian cysts (166). Use of OCs also

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helps relieve dysmenorrhea (166). Oral contraceptives offer effective therapy for women with menorrhagia and dysfunctional uterine bleeding (163).

All combination OCs offer some protection from functional ovarian cysts, but multiphasic preparations offer less protection than other forms of combination OCs (167). Oral contraceptives also appear to decrease the risk of developing leiomyomata (168).

All combination OCs reduce circulating androgen levels and usually improve acne. Two OCs have been specifically FDA approved for acne treatment: the *norgestimate/EE triphasic* (*TriCyclen*) and a *norethindrone/EE multiphasic* (*Estrostep*) (163).

There is growing evidence that OC use is protective against colon cancer. A case-control study in Italy comparing women with colon cancer with controls found a 37% reduction in colon cancer and a 34% reduction in rectal cancer (colon cancer OR, 0.63; 95% CI 0.45–0.87 and rectal cancer OR, 0.66; 95% CI 0.43–1.01). Longer use produced more protection against colon cancer (169). Results of the U.S. Nurses Health Study also disclosed some degree of protection. Women who had used OCs for 96 months or more had a 40% lower risk of colorectal cancer (RR, 0.60; 95% CI, 1.15–2.14) (170). The mechanism of protection has not been identified.

Fertility after OC Use

After discontinuing OCs, return of ovulatory cycles may be delayed for a few months. Women who have amenorrhea more than 6 months after discontinuation of OCs should undergo a full evaluation because of the risk for prolactin-producing pituitary tumors. This risk is not related to OC use but rather to the probability that the slow-growing tumor was already present and produced menstrual irregularity, prompting the patient to take OCs (171).

Sexuality

In a study that recorded all episodes of female-initiated sexual behavior throughout the menstrual cycle, an increase in sexual activity at the time of ovulation was noted. This increase was not present in women who were taking OCs (172).

Teratogenicity

A meta-analysis of 12 prospective studies, including 6,102 women who used OCs and 85,167 women who did not, revealed no increase in overall risk for malformation, congenital heart defects, or limb reduction defects with the use of OCs (173). Progestins have been used to prevent miscarriage. A large study compared women showing signs of threatened abortion who were treated with progestins (primarily *medroxyprogesterone acetate*) with women who were not treated. The rate of malformation was the same among the 1,146 exposed infants as among the 1,608 unexposed infants (174). Conversely, estrogens taken in high doses in pregnancy can induce vaginal cancer in exposed female offspring in utero.

Interaction of Oral Contraceptives with Other Drugs

Some drugs (e.g., rifampin) reduce the effectiveness of oral contraceptives; conversely, OCs can augment or reduce the effectiveness of other drugs (e.g., benzodiazepines) (175,176). Perhaps of greatest clinical significance are six antiepileptic drugs: *phenytoin*, *phenobarbital*, *carbamazepine*, *oxcarbazepine*, *felbamate*, and *topiramate* (177). These drugs and the antibiotic *rifampin* all induce synthesis of liver cytochrome P450 enzymes and reduce plasma levels of *EE* in women taking OCs, increasing the likelihood of contraceptive failure (175). Several other antiseizure agents have no effect on the levels of contraceptive steroids in the blood. These agents include *valproic acid*, *vigabatrin*, *lamotrigine*, *gabapentin*, *tiagabine*, *levetiracetam*, *zonisamide*, *ethosuximide*, and the *benzodiazepines* (177). *St. John's wort* induces cytochrome P450 as well and is reported to increase clearance of *EE* and *norethindrone* (178). The antifungal agents *griseofulvin*, *ketoconazole*, and *itraconazole* also induce these hepatic enzymes and may reduce OC efficacy (176). *Ampicillin* and *tetracycline* have been implicated in numerous case reports of OC failure. They kill gut bacteria (primarily clostridia) that are responsible for hydrolysis of steroid glucuronides in

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the intestine, which allows reabsorption of the steroid through the enterohepatic circulation. In human studies, however, it has not been possible to demonstrate reduced plasma levels of *EE*. Although women taking OCs who will be treated with antibiotics are commonly advised to use condoms as well, controlled studies of OC users have found no difference in pregnancy rates with exposure to *penicillins*, *cephalosporins*, and *tetracyclines* (179). *Nevirapine* reduces blood levels of both *EE* and *norethindrone*. Oral contraceptives should not be the primary method of contraception for women treated with this drug (180).

Certain drugs actually appear to increase plasma levels of contraceptive steroids. Ascorbic acid (vitamin C) and acetaminophen may elevate plasma *EE*.

An example of OCs affecting the metabolism of other drugs is seen with diazepam and related compounds. Oral contraceptive use reduces the metabolic clearance and increases the half-life of those *benzodiazepines* that are metabolized primarily by oxidation: *chlor-diazepoxide*, *alprazolam*, *diazepam*, and *nitrazepam*. *Caffeine* and *theophylline* are metabolized in the liver by two of the P450 isozymes, and their clearance is also reduced in OC users. *Cyclosporine* is hydroxylated by another of the P450 isozymes, and its plasma concentrations are increased by OCs. Plasma levels of some analgesic drugs are decreased in OC users. *Salicylic acid* and *morphine* clearances are enhanced by OC use; therefore, higher doses could be needed for adequate therapeutic effect. Clearance of *ethanol* may be reduced in OC users.

Oral Contraceptives and Clinical Chemistry Alterations

Oral contraceptives have the potential to alter a number of clinical laboratory tests as a result of estrogen-induced changes in hepatic synthesis; however, a large study comparing OC users with pregnant and nonpregnant controls found minimal changes (181). Hormone users took a variety of OCs containing 50 to 100 µg of estrogen, higher doses than are used today. **Compared with nonpregnant women who were not using OCs, the OC users had an increase in T₄ that is explained by increased circulating thyroid-binding protein**, no change in creatinine and globulin levels, slight reduction in mean fasting glucose values and serum glutamic oxaloacetic transaminase, and a decrease in total bilirubin and alkaline phosphatase.

Choice of Oral Contraceptives

The oral contraceptives currently available in the United States are listed in Table 10.7. With the introduction of OCs containing the new progestins, new preparations with 20 µg of *EE*, new variations of multiphasic preparations, plus branded generic formulations of older OCs, an array of choices are possible.

The lowest-dose OCs all contain the same amount of the same estrogen, 20 µg of *EE*. However, the amount of progestins they contain differs: *norethindrone acetate*, *levonorgestrel*, *desogestrel*, or *norgestimate* (Table 10.7). The first 20-µg *EE* OC (*LoEstrin 1-20*) contained 1 mg *norethindrone acetate*. A comparison of this OC with a triphasic OC with 35 µg of *EE* and *norgestimate* (*Tri-Cyclen*) found considerable more breakthrough bleeding and spotting and more episodes of missed menses with the 20-µg *norethindrone acetate/EE* than with the higher-estrogen OC containing *norgestimate*. There was no difference in compliance, discontinuation rates, or adverse events (182). In a three-way trial, the 35-µg *norgestimate/EE* triphasic OC (*Tri-Cyclen*) was compared with two new 20-µg *EE* pills, one containing 100 µg of *levonorgestrel* (*Allese*), the other containing 150 µg *desogestrel*, followed by 2 hormone-free days and 5 days of 10 µg *EE* per day (*Mircette*) (183). Contraceptive efficacy was not significantly different. Women starting on OCs had more breakthrough bleeding and bleeding in the second half of the cycle with *Allese* than with the other two OCs in the first two cycles, but thereafter there was little difference except that *Mircette* users had more breakthrough bleeding in cycle 4. Women taking *Tri-Cyclen* consistently experienced more frequent estrogenic side effects of bloating, breast tenderness, and nausea than did women taking either 20-µg *EE* OC. These authors concluded that for the specific OCs evaluated, changing to the lowest estrogen dose was beneficial.

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Table 10.7 Composition of Oral Contraceptives in Current Use in the United States, 2005

<i>Trade Name^a</i>	<i>Progestin</i>	<i>Estrogen</i>
Progestin-only		
<i>Micronor</i> (<i>Errin, Jolivette, Camila, Nora-BE, NorQD</i>)	NE 350 µg	none
<i>Ovrette</i>	d,l-NG 75 µg	none
Combination-monophasic		
<i>Norlestrin</i>	NEA 2.5 mg	EE 50 µg
<i>Norlestrin-1</i>	NEA 1.0 mg	EE 50 µg
<i>Loestrin 1.5/30</i>	NEA 1.5 mg	EE 30 µg
<i>Ovral</i> (<i>Ogestrel</i>)	d,l-NG 0.5 mg	EE 50 µg
<i>Lo Ovral</i> (<i>Low-Ogestrel, Cryselle</i>)	d,l-NG 0.3 mg	EE 30 µg
<i>Nordette</i> (<i>Levlen, Levora 0.15/30, Portia</i>) <i>Seasonale</i> contains the same steroids, but provides 84 active pills in each package rather than 21	levoNG 0.15 mg	EE 30 µg
<i>Ortho-Novum 1/50, Norinyl 1/50, Necon 1/50, Nelova 1/50 M</i>)	NE 1.0 mg	ME 50 µg
<i>Ovcon 50</i>	NE 1.0 mg	EE 50 µg
<i>Orthonovum 1/35</i> (<i>Norinyl 1/35, Necon 1/35, Nelova 1/35E, Nortrel 1/35</i>)	NE 1.0 mg	EE 35 µg
<i>Modicon</i> (<i>Brevicon, Necon 0.5/35, Nelova 0.5/35E, Nortrel 0.5/35</i>)	NE 0.5 mg	EE 35 µg
<i>Ovcon 35</i>	NE 0.4 mg	EE 35 µg
<i>Demulen 1/50</i> (<i>Zovia 1/50E</i>)	ED 1.0 mg	EE 50 µg
<i>Demulen 1/35</i> (<i>Zovia 1/35E</i>)	ED 1.0 mg	EE 35 µg
<i>Desogen</i> (<i>Orthocept, Apri, Solia</i>)	Deso 0.15 mg	EE 30 µg
<i>OrthoCyclen</i> (<i>MonoNessa, Previfem, Sprintec</i>)	Norg 0.25 mg	EE 35 µg
<i>Loestrin 1/20</i>	NEA 1.0 mg	EE 20 µg
<i>Allese</i> (<i>Levlite, Aviane, Lessina</i>)	levoNG 0.10 mg	EE 20 µg

Multiphasic*Orthonovum 10/11 (Neocon 10/11, Nelova 10/11)*

NE 0.5 mg and EE 35 µg (first 10 days)

NE 1.0 mg and EE 35 µg (next 11 days)

Orthonovum 7/7/7 (Necon 7/7/7, Nortrel 7/7/7)

NE 0.5 mg and EE 35 µg (first 7 days)

NE 0.75 mg and EE 35 µg (next 7 days)

NE 1.0 mg and EE 35 µg (last 7 days)

Triphasil (Enpresse, Trilevlen, Trivora)

Levo NG 0.050 mg and EE 30 µg (first 6 days)

Levo NG 0.075 mg and EE 40 µg (next 5 days)

Levo NG 0.125 mg and EE 30 µg (last 10 days)

Tri-Norinyl

NE 0.5 mg and EE 35 µg (first 7 days)

NE 1.0 mg and EE 35 µg (next 9 days)

NE 0.5 mg and EE 35 µg (next 5 days)

OrthoTri-Cyclen (TriNessa, Tri-Sprintec, Tri-Previfem)

Norg 0.18 mg and EE 35 µg (first 7 days)

Norg 0.215 mg and EE 35 µg (next 7 days)

Norg 0.250 mg and EE 35 µg (next 7 days)

Ortho Tri-Cyclen Lo

Norg 0.18 mg and EE 25 µg (first 7 days)

Norg 0.215 mg and EE 25 µg (next 7 days)

Norg 0.250 mg and EE 25 µg (next 7 days)

Estrostep

NEA 1.0 mg and EE 20 µg (first 5 days)

NEA 1.0 mg and EE 30 µg (next 7 days)

NEA 1.0 mg and EE 35 µg (next 9 days)

Mircette (Kariva)

Deso 0.15 mg and EE 20 µg (first 21 days)

Placebo and placebo (next 2 days)

Placebo and EE 10 µg (next 5 days)

^a Trade names are used for ease of identification. A second or third identical formulation by a different manufacturer is identified in parenthesis. Most formulations are available either as a 21-day or 28-day package. The 28-day package has 7 placebo tablets.

Some formulations add iron, usually ferrous fumarate, to each of the 7 placebo tablets in a 28-day package. EE, ethinyl estradiol; ME, mestranol; NE, norethindrone; NEA, norethindrone acetate; ED, ethynodiol diacetate; d,l-NG, d,l-norgestrel; levoNG, levonorgestrel; Deso, desogestrel; Norg, norgestimate.

Oral contraceptives can be taken continuously for an indefinite time by discarding the placebo tablets from each pack. Continuous oral contraceptive use has been prescribed for endometriosis, pelvic pain, and bleeding disorders. *Seasonale* provides the same low dose of *levonorgestrel* and *EE* found in *Nordette* and several other OCs, but packages 84 active tablets with 7 placebos for continuous use with one withdrawal bleed every 4 months (184).

For the average patient, the first choice of preparation for contraceptive purposes is a low-estrogen OC (25–35 µg of EE) or a very-low-estrogen OC (20 µg EE).

Breakthrough bleeding and spotting are common at first and generally improve with time. If the problem persists, it may be relieved by changing from a multiphasic to monophasic version at the same estrogen level.

If bleeding remains a problem, a temporary increase in estrogen should be tried: 20 µg of EE daily for 7 days while continuing the OC (185).

Side effects—nausea, breast tenderness, mood changes, and weight gain—are less common with current formulations than with previous OCs and usually resolve after the first few cycles.

If symptoms persist, the lowest-dose, most effective formulations could be tried (i.e., those containing only 20 µg of EE).

In patients who have persistent breast tenderness, the type of OC could be changed to one with more progestin activity, for example, the 20- to 30-µg

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EE pills that contain *levonorgestrel*. Oral contraceptives that contain high-potency progestin produce fewer breast symptoms

Nausea is generally related to the estrogen component, and changing to a 20-µg EE preparation may be beneficial. The patient should be reminded to expect spotting and breakthrough bleeding at first when changing to a lower-dose OC.

Patients with apparent weight gain from fluid retention while taking OCs, or with hirsutism or acne that has not responded to other OCs, may benefit from a change to the *drospirenone/EE* pill.

Transdermal Hormonal Contraception

The *OrthoEvra* patch and the *NuvaRing* both provide combinations of ultrapotent progestins with EE. Both patch and ring provide almost constant low levels of the contraceptive steroids that are considerably less than peak levels seen with OCs. Both offer greater convenience to the user, which improves compliance. Because both contain estrogen, the concerns about venous thrombosis and vascular disease with OCs must be considered to apply to these methods as well.

The patch has a surface area of 20 cm². It delivers a daily dose of 150 µg norelgestromin, the active metabolite of norgestimate, and 20 µg of EE. The patch is worn for 1 week, then replaced with a new patch for 7 days, continuing for 3 consecutive weeks followed by a week with no patch. The patch was compared with an multiphasic OC containing *levonorgestrel*, 50 to 125 µg, and 30 to 40 µg EE (*Triphasil*) in a randomized trial of 1,417 women (95). The overall and method failure Pearl Index were 1.24 and 0.99 pregnancies per 100 woman-years in the patch group and 2.18 and 1.23 in the OC group, respectively, and numerically less in the patch group but not statistically significant. **Patch users had more breakthrough bleeding/spotting in the first two cycles, but thereafter this did not differ from the OC users.** Patch users reported more breast discomfort, dysmenorrhea, and abdominal pain than the OC users, but other adverse events were uncommon and did not differ. Importantly, perfect compliance was reported for 88.2% of patch users' cycles versus 77.7% of the pill users' cycles ($p < 0.001$). Pregnancy risk appears to be higher for women weighing more than 90 kg.

The *NuvaRing* is 54 mm in outer diameter and has a cross section of 4 mm. It delivers daily doses of 120 µg of *etonogestrel*, the active metabolite of *desogestrel*, with 15 µg of *EE*. The soft, flexible ring is worn in the vagina for 3 weeks, and then removed for 1 week, after which time a new ring is inserted. In a pharmacokinetic study comparing the ring with a combination OC containing 150 µg of *desogestrel* and 30 µg of *EE*, maximum blood levels of *EE* with the ring were about one third of those seen with the OC, and the *etonogestrel* level was about 40% of that produced by the OC. Despite these findings, ovulation was inhibited in all women studied (96). **Women wearing the ring are reported to have fewer days of irregular bleeding/spotting than women taking an OC** with 150 µg of *levonorgestrel* and 30 µg of (186). A large study found a total pregnancy rate of 1.18 (95% CI 0.73–1.80) per 100 woman-years and 0.77 (0.37–1.40) pregnancies per 100 woman-years with perfect use (187). Some women prefer to remove the ring for intercourse, although this is not necessary. It should be reinserted within 3 hours to avoid loss of efficacy.

Injectable Hormonal Contraceptives

Depomedroxyprogesterone Acetate

Depomedroxyprogesterone acetate (DMPA), a suspension of microcrystals of a synthetic progestin, was approved for contraception in 1992. A single 150-mg intramuscular dose

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will suppress ovulation in most women for 14 weeks or longer (188). **The regimen of 150 mg every 3 months is highly effective, producing pregnancy rates of about 0.3 per 100 women per year.** Probably because of the high blood levels of the progestin, efficacy appears not to be reduced by administration of other drugs and is not dependent on the patient's weight. Women treated with *DMPA* experience disruption of the menstrual cycle and have initial spotting and bleeding at irregular intervals. Eventually, total amenorrhea develops in most women who take *DMPA*; with continued administration, amenorrhea develops in 50% of women by 1 year and in 80% by 3 years (Fig. 10.12). **Persistent irregular bleeding can be treated by adding low-dose estrogen temporarily;** for example, conjugated estrogens, 1.25 mg per day, can be given for 10 to 21 days at a time. Irregular bleeding with *DMPA* may be related to the downregulation of endometrial estrogen receptors it produces. Treatment with 50 mg of mifepristone every 2 weeks increases endometrial estrogen receptors and reduces breakthrough bleeding in new users of both *DMPA* and progestin implants (189). *Depomedroxyprogesterone acetate* persists in the body for several months in women who have used it for long-term contraception, and return to fertility may be delayed. In a large study, however, 70% of former users desiring pregnancy conceived within 12 months, and 90% conceived within 24 months (190).

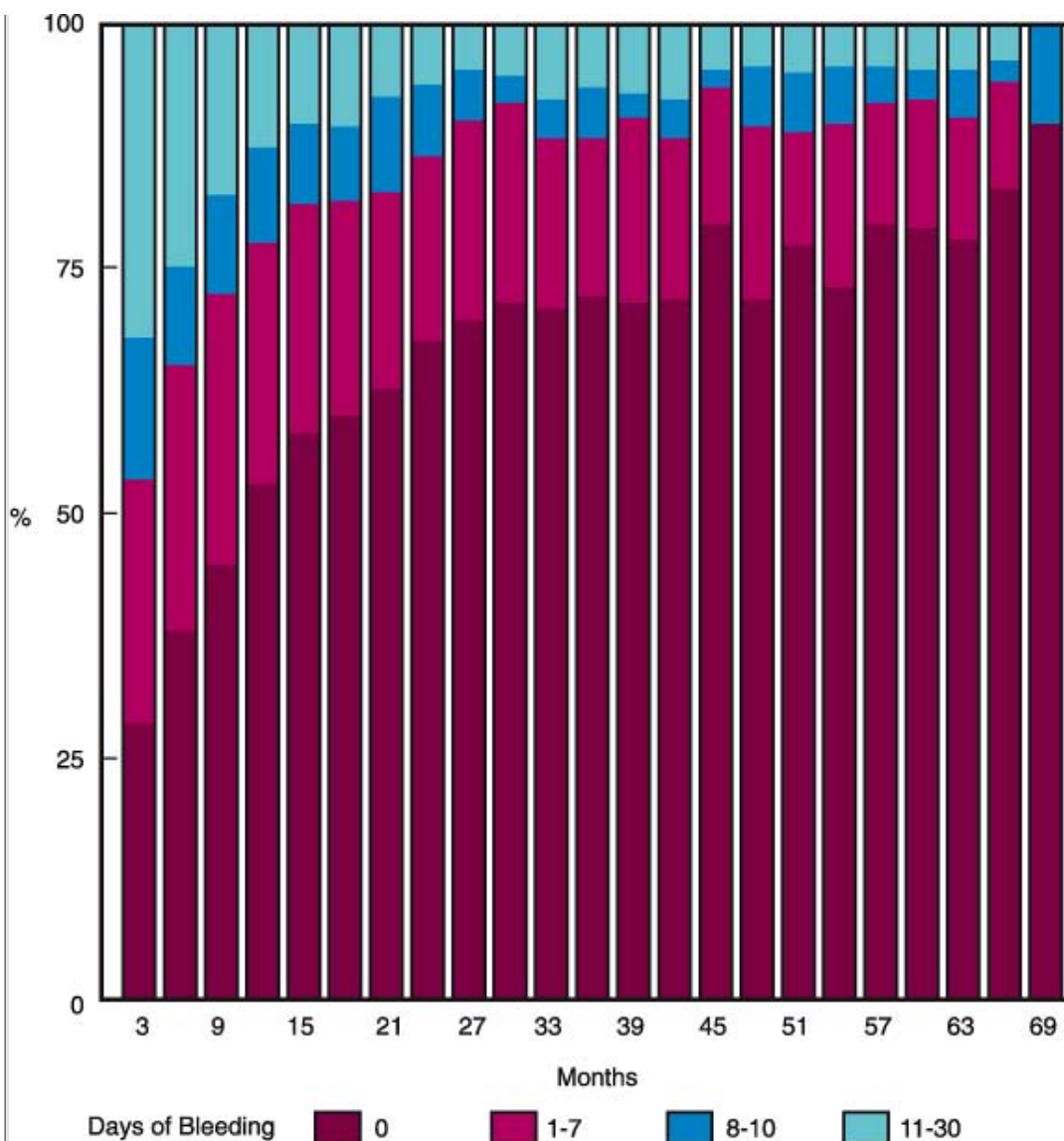


Figure 10.12 Bleeding pattern and duration of use of depomedroxyprogesterone acetate (DMPA): percentage of women who have bleeding, spotting, or amenorrhea while taking DMPA 150 mg every 3 months. (From Schwallie PC, Assenzo JR. Contraceptive use-efficacy study utilizing *medroxyprogesterone acetate* administered as an intramuscular injection once every 90 days. *Fertil Steril* 1973;24:331-339, with permission.)

Safety

Depomedroxyprogesterone acetate suppresses ovarian estrogen production, which could be expected to affect bone density. Prospective studies have demonstrated bone loss during *DMPA* therapy, with recovery of bone mass after *DMPA* use is discontinued (191). Similar bone loss and then recovery occurs with lactation. Adolescents are of especial concern because they normally gain bone mass; in fact, most of adult bone mass is attained by age 20. A small study comparing *DMPA* with implant or OC users found that *DMPA* blocked the usual rapid increase in bone density normally seen in adolescents (167,192). Estrogen injections prevented the bone loss and allowed adolescent women to gain bone density despite use of *DMPA*. The FDA has issued a "black box warning" proposing that *DMPA* treatment be limited to 2 years at a time unless the patient has no other good options for contraception.

The effect of *DMPA* on plasma lipids has been inconsistent; in general, *DMPA* users appear to

have reduced total cholesterol and triglyceride levels, slight reduction in HDL cholesterol, and no change or slight increase in LDL cholesterol, all of which are consistent with a reduction in circulating estrogen levels. In some studies, the decrease in HDL and increase in LDL are statistically significant, although the values remain within normal ranges (193). The use of *DMPA* has not been associated with myocardial infarction. Glucose tolerance tests disclose a small elevation of glucose in *DMPA* users. There is no change in hemostatic parameters, with the exception that antithrombin III levels are sometimes found to be reduced with chronic therapy (193). *DMPA* has not been linked to thrombotic episodes in women of reproductive age. However, thrombotic episodes have occurred in elderly women with advanced cancer who were treated with a variety of agents, including *DMPA* and *tamoxifen* (194,195). Such patients are at high risk for thrombosis regardless of the use of *DMPA*. Women taking *DMPA* appear to experience a weight gain of 2 to 3 pounds more than nonusers over several years. Its use has not been associated with teratogenesis. It is safe for use by lactating women and, as with other progestin-only hormonal methods, appears to increase milk production. *Depomedroxyprogesterone acetate* has not been associated with affective disorders or mood changes, although the data are limited (196,197).

Benefits

***Depomedroxyprogesterone acetate* appears to have many of the noncontraceptive benefits of combination oral contraceptives** (184). Decreases in anemia, PID, ectopic pregnancy, and endometrial cancer have been reported. No association between *DMPA* and cervical cancer has been demonstrated (198). Ovarian cancer has been found to be unrelated to the use of *DMPA* (199). The risk of breast cancer during the first 4 years of use appears to be slightly increased, but there is no relation to long-term use and no overall increase in breast cancer risk; hence, any causal relationship between *DMPA* and breast cancer is unlikely (200).

Subcutaneous *DMPA*

Depo-subQ Provera 104, a new lower-dose *DMPA* preparation for subcutaneous administration, received FDA approval in 2005. The total dose is 30% less than that of the older *DMPA* intramuscular preparation. Because the dose is administered subcutaneously, blood levels are adequate to completely suppress ovulation for more than 13 weeks in all subjects tested, with a mean time of 30 weeks for return to ovulatory function (201). **Contraception efficacy is superb, with no pregnancies in a total of 16,023 woman-cycles in the phase three studies done in the United States** (202). Blood levels were lower in very obese women but still sufficient to suppress ovulation completely. The weight gain reported with the 150 mg *DMPA* remained a problem with the lower dose *DMPA*: Mean weight gain was 3.5 lb in the first year of use. Unfortunately, loss of bone density was observed with this dosage of *DMPA*, as with the larger intramuscular

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dose. The FDA warning still applies against use beyond 2 years unless other methods of contraception are inadequate for the patient.

Once-a-Month Injectable

A once-a-month injectable contraception containing only 25 mg of *DMPA* in combination with 5 mg of the long-acting estrogen *estradiol cypionate* was briefly available in the United States, but was withdrawn by the manufacturer because of a packaging problem (184). Originally developed by the World Health Organization, it is described as *CycloFem* or *CycloProvera* in the literature and was marketed in the United States as *Lunelle* (203). Given once a month, this combination produces excellent contraceptive effects. Monthly withdrawal bleeding is similar to

a normal menses, leading to high continuation rates despite the need for a monthly injection (204). Whether it will be reintroduced into the United States is uncertain.

Subdermal Implants

Levonorgestrel subdermal implants are no longer available in the United States. The original *Levonorgestrel* implant (*Norplant*) consisted of six rods.

A two-rod version (*Jadelle*[™], *Norplant II*) is as effective as *Norplant* and easier to insert and remove (205). The two-rod system is marketed in Europe and has been approved by the FDA, but it currently is not marketed in the United States.

Implanon is a single-rod subdermal system containing *etonogestrel*, the metabolite of *desogestrel* used in the *NuvaRing*. **FDA approval is expected soon. The implant releases 60 µg of etonogestrel per day, enough to completely inhibit ovulation for at least 3 years.** The single-rod system is easily inserted and removed. In the United States trial, mean time for insertion was only 0.5 minute, and removal required a mean time of 3.5 minutes (206). There were no pregnancies in 474 woman-years of use. **In fact, no pregnancies have occurred in worldwide clinical trials including many thousands of women.** Irregular bleeding is a problem but occurs most frequently in the first 90 days of use and decreases over time. This is the main reason given by women for discontinuing use. The other most commonly reported side effects are headache, vaginitis, acne, dysmenorrhea, and emotional lability. In the United States trial, with 330 women participating, two adverse effects were considered serious and possibly related to the implant: one ruptured ovarian follicular cyst and one acute exacerbation of depression (206). **The etonogestrel implant offers amazing efficacy and convenience, and because it contains no estrogen, it should not be associated with an increased risk of thrombosis.**

Emergency Contraception

Implantation of the fertilized ovum is believed to occur on the sixth day after fertilization. This interval provides an opportunity to prevent pregnancy even after fertilization occurs. Prevention of pregnancy can be accomplished using hormonal agents, singly or in combination, or IUDs.

Estrogens

The principle of emergency contraception was first demonstrated with high-dose estrogen, which taken within 72 hours of coitus prevents pregnancy. The mechanism of action of postcoital estrogen use may involve altered tubal motility, interference with corpus luteum function mediated by prostaglandins, or alteration of the endometrium. In an analysis of more than 3,000 women treated after coitus with 5 mg of *EE* daily for 5 days, the pregnancy rate was 0.15% (207).

Estrogen and Progestin in Combination

High-dose estrogen was replaced by the combination of *EE* 0.200 mg and *levonorgestrel* 2 mg (2 *Ovral* tablets followed by 2 more tablets 12 hours later), as first described by

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Yuzpe (208). The average pregnancy rate with this method is 1.8%, but it is 1.2% if treatment is started within 12 hours of intercourse (209). Nausea and vomiting are common with both regimens, and an antiemetic usually is prescribed. A comparable dose of *EE* and *levonorgestrel* is provided by taking 4 tablets of *LoOvral*, *Nordette*, *Levlen*, *Triphasil*, or *TriLevlen*, or 5 tablets of *Allese* instead of 2 tablets of *Ovral*. A single study has compared a combination

OC regimen providing *norethindrone*, 2 mg, and *EE* to the Yuzpe method and found the norethindrone OCs to be as effective (210).

Levonorgestrel Alone

Levonorgestrel alone, 0.75 mg initially followed by another 0.75 mg 12 hours later, is more effective than the combination of *EE* and lower-dose *levonorgestrel* and is clearly the emergency contraceptive method of choice at present. This preparation is sold in the United States as Plan B. **The World Health Organization conducted a randomized trial with 1,998 women assigned to the Yuzpe method or to *levonorgestrel* alone**, started within 72 hours of intercourse. The pregnancy rate was 3.2% with the Yuzpe method, and only 1.1% with *levonorgestrel* alone (RR for pregnancy, 0.32; 95% CI, 0.18–0.70). Nausea and vomiting occurred much less frequently with *levonorgestrel* alone (23.1% versus 50.5%, and 5.6% versus 18.8%, respectively) (211). The efficacy of both methods declines as time since intercourse increases. Even after 49 to 72 hours, however, the pregnancy rate with the *levonorgestrel* treatment was only 2.7% (Fig. 10.13). A single dose of 1.5 mg *levonorgestrel* is just as effective as two doses of 0.75 mg, has no more side effects, and is more convenient for the patient (212). There is evidence these doses of *levonorgestrel* have almost as much efficacy at 3 to 5 days after intercourse; hence, women who present after 3 days but before 5 days should not be refused treatment.

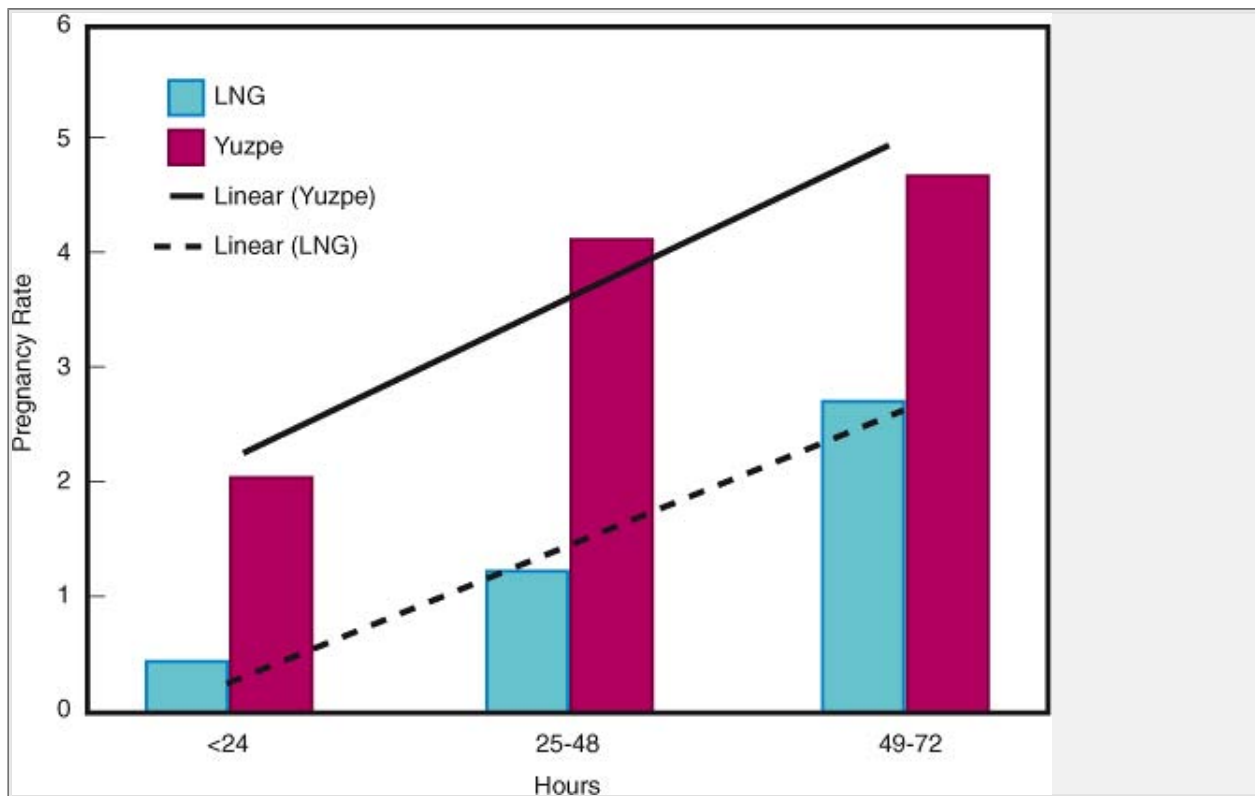


Figure 10.13 Emergency contraception: pregnancy rates by treatment group and time since unprotected coitus. LNG is levonorgestrel, 0.75 mg \times 2. Yuzpe method is ethinyl estradiol, 0.100 mg plus levonorgestrel 0.50 mg \times 2, 12 hours later. (From **Anonymous**. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task Force on Postovulatory Methods of Fertility Regulation. *Lancet* 1998;352:430 [modified from Table 3], with permission.)

Four cases of cerebrovascular events have been reported in women who used the Yuzpe method. One of them had preexisting severe migraine. No cerebrovascular complications have

been reported with *levonorgestrel* emergency contraception. Neither deep vein thrombosis nor pulmonary embolism has been reported with either method (213).

Copper Intrauterine Device

Postcoital insertion of a copper IUD within 7 days appears to be even more effective than steroids for emergency contraception (214). In 879 patients treated with an IUD, only one pregnancy occurred (207). No pregnancies occurred during the first month after insertion of copper IUDs as long as 7 days after coitus. It is likely that the *levonorgestrel* IUD would also work for this purpose, but there are as yet no studies of its use after coitus.

Danazol

A weak androgen, *danazol* has also been used for emergency contraception. The pregnancy rate was 2% among 998 women (207). *Levonorgestrel* is a better choice because of low cost and fewer side effects.

Mifepristone

The antiprogestone *mifepristone* (*RU486*) is also highly effective for postcoital contraception and appears to have no significant side effects. The usual abortifacient dose is 200 mg, but a dose of only 10 mg is effective for emergency contraception. In one study, 2,065 women were randomized to either *mifepristone*, 10 mg, or *levonorgestrel*, two doses of 0.75 mg, and included women up to 120 hours after intercourse (215). The crude pregnancy rate was 1.3% for *mifepristone* and 2.0% for *levonorgestrel* ($p = 0.46$). Side effects were the same, and both methods were judged highly acceptable by the subjects. *Mifepristone* is also highly effective in inducing menstruation when taken on day 27 of the menstrual cycle, well beyond the 72- to 120-hour window usually considered for postcoital contraception. Of 62 women treated in this fashion with 600 mg of *mifepristone*, only one conceived (207).

Contraception for Women with Chronic Illness

Women with chronic illness may present special problems that should be considered in the choice of a method of contraception. The illness may make pregnancy more complicated and dangerous for these women, thus making effective contraception all the more important. Some common conditions and considerations about contraception are listed in Table 10.8. **For many women, an important strategy is to prescribe a progestin-only method and to avoid estrogen-containing hormonal contraceptives** (184).

Hormonal Contraception for Men

The same negative feedback of sex steroids that can block ovulation in women will also suppress spermatogenesis in men, but it will produce loss of libido and potentially extinguish sexual performance. The principle was first demonstrated in 1974 using oral estrogen and methyl testosterone (216). Testosterone given alone can suppress sperm production to very low levels while maintaining normal libido and sexual performance. Over many years investigators have studied long-acting testosterone salts for male contraception (217,218). Ethnicity is an important predictor of efficacy of sperm suppression with testosterone therapy. Asian men virtually always achieve azospermia or oligospermia when treated with testosterone undecanoate, 500 to 1,000 mg monthly, whereas only 86% of white men achieved oligospermia or azospermia with similar testosterone regimens (218). However, pregnancy has occurred in partners of androgen-treated oligospermic men with sperm counts as low as 3 million/mL (219).

Combining testosterone with a progestin allows a lower dose of the androgen with efficacy comparable to use of testosterone alone. One promising regimen combined injections of

testosterone undecanoate with *norethindrone enanthate* given at 6-week intervals. This regimen produced azospermia in 90% of subjects (220). Adverse lipid changes have been noted with *DMPA* and androgen combinations, raising concern about vascular disease with prolonged use. Liver cancer is also a concern with long-term androgen therapy (221).

Table 10.8 Contraception for Women with Chronic Illness

Psychiatric disorders

- OCs, implants, *DMPA*, and IUDs are good choices.
- Use of barrier methods should be encouraged to decrease risk for STDs.

Coagulation disorders

- Hemorrhagic disorders: OCs may be indicated to prevent hemorrhagic ovarian cysts and menstrual hemorrhage.
- Thrombotic disorders: Avoid estrogen-containing OCs.

Dyslipidemia

- May use low-dose OCs if lipid abnormality is successfully managed by diet or drug therapy, but lipids should be monitored at 3–6 months.
- Avoid OCs if triglycerides are elevated.
- Select less androgenic OCs.
- Progestin-only OCs, *DMPA*, and IUDs are acceptable.

Hypertension

- Young women with no other risk factors with well-controlled hypertension may use low-dose OCs under close supervision.
- Older women, smokers, and those with poorly controlled hypertension should probably avoid combination OCs.
- *DMPA*, *Norplant*, IUDs, and progestin-only OCs are good alternatives.

Diabetes

- Young diabetic women without vascular disease can use low-dose OCs.
- Older women or women with vascular disease probably should not use combination OCs.
- *DMPA*, *Norplant*, IUDs, and progestin-only OCs are good alternatives.

Headache

- Migraine without aura, without neurologic symptoms, does not rule out OCs if use is closely supervised.
- *Norplant* and *DMPA* may be used safely.

Epilepsy

- OCs do not increase the risk for seizure, but antiseizure drugs reduce efficacy of OCs and *Norplant*.
- OCs with 50 µg estrogen can be used, as can *DMPA*. IUDs are not contraindicated.

DMPA, depomedroxyprogesterone acetate; IUD, intrauterine device; OCs, oral contraceptives; STDs, sexually transmitted diseases.

From **Association of Reproductive Health Professionals**. *Clinical challenges in contraception: a program on women with special medical conditions*. Clinical proceedings. Washington, DC: ARHP, 1994.

Sterilization

Surgical sterilization is the most common method of fertility control used by couples in

the United States (4). Laparoscopic techniques for women and vasectomy for men are safe and readily available throughout the United States. The mean age at sterilization is 30 years. Age younger than 30 years when sterilized and divorce and remarriage are predictors of sterilization regret, which may lead to a request for reversal of sterilization (222).

Female Sterilization

Hysterectomy is no longer considered for sterilization because morbidity and mortality are too high in comparison with tubal sterilization. Vaginal tubal sterilization, which has been associated with occasional pelvic abscess, is rarely performed in the United States. Five procedures are used in the United States.

- Tubal sterilization at the time of laparotomy for a cesarean delivery or other abdominal operation
- Postpartum minilaparotomy soon after vaginal delivery
- Interval minilaparotomy
- Laparoscopy
- Hysteroscopy

Postpartum tubal sterilization at the time of cesarean delivery adds no risk other than a slight prolongation of operating time; however, cesarean birth poses more risk than vaginal birth, and planned sterilization should not influence the decision to perform a cesarean delivery. Minilaparotomy can be performed in the immediate postpartum state. The uterus is enlarged, and the fallopian tubes lie in the midabdomen, easily accessible through a small, 3- to 4-cm subumbilical incision.

Interval minilaparotomy, first described by Uchida (223), was rediscovered and popularized in the early 1970s in response to the increased demand for sterilization procedures and a simpler alternative to laparoscopy. In the nongravid state, the uterus and tubes lie deep in the pelvis. A short transverse suprapubic incision is made, and the uterus and tubes are then elevated upward, just beneath the incision, by use of a uterine-elevating probe placed into the uterine cavity through the vagina. Interval minilaparotomy is usually performed as an outpatient procedure and can be accomplished readily with local anesthesia and conscious sedation.

Surgical Technique

The procedure usually elected for tubal sterilization is the Pomeroy or modified Pomeroy technique (Fig. 10.14). In the classic Pomeroy procedure, a loop of tube is excised after ligating the base of the loop with a single absorbable suture. A modification of the procedure is excision of the midportion of the tube after ligation of the segment with two separate absorbable sutures. This modified procedure has several names: *partial salpingectomy*, *Parkland Hospital technique*, *separate sutures technique*, and *modified Pomeroy*. In the Madlener technique, now abandoned because of too many failures, a loop of tube is crushed by cross-clamping its base, ligated with permanent suture, and then excised. **Pomeroy and partial salpingectomy procedures have failure rates of 1 to 4 per 1,000 cases** (224). **In contrast, pregnancy is almost unheard of after tubal sterilization by the Irving**

or **Uchida methods** (223,225). In the Irving method, the midportion of the tube is excised, and the proximal stump of each tube is turned back and led into a small stab wound in the wall of the uterus and sutured in place, creating a blind loop. With the Uchida method, a *saline-epinephrine* solution (1:1,000) is injected beneath the mucosa of the midportion of the tube, separating the mucosa from the underlying tube. The mucosa is incised along the antimesenteric border of the tube, and a tubal segment is excised under traction so that the ligated proximal stump will retract beneath the mucosa when released. The mucosa is then closed with sutures, burying the proximal stump and separating it from the distal stump. In Uchida's personal series of more than 20,000 cases, there were no pregnancies (223).

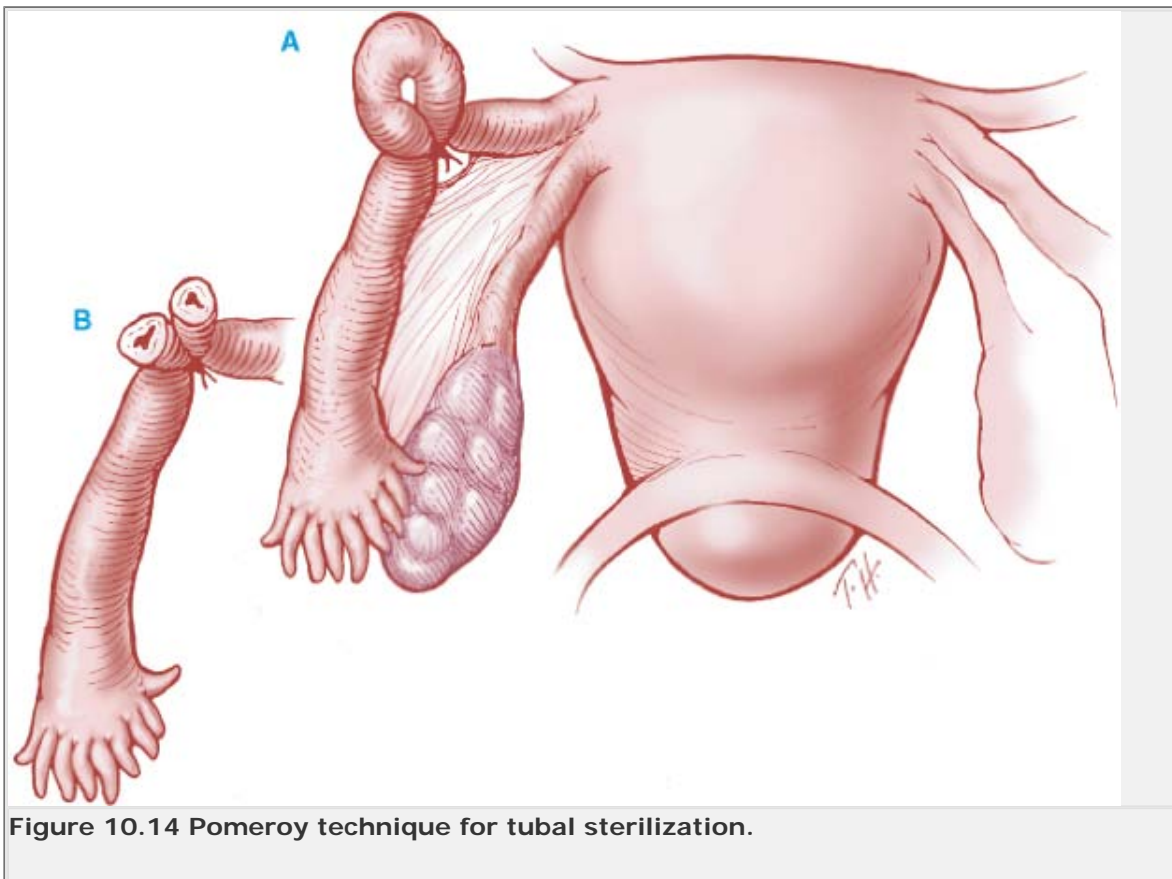


Figure 10.14 Pomeroy technique for tubal sterilization.

Laparoscopy

In the standard laparoscopy technique, the abdomen is inflated with a gas (carbon dioxide or nitrous oxide) through a special needle inserted at the lower margin of the umbilicus (226). A hollow sheath containing a pointed trocar is then pushed through the abdominal wall at the same location, the trocar is removed, and the laparoscope is inserted into the abdominal cavity through the sheath to visualize the pelvic organs. A second, smaller trocar is inserted in the suprapubic region to allow the insertion of special grasping forceps. Alternatively, an operating laparoscope that has a channel for the instruments can be used; thus, the procedure can be performed through a single small incision. Laparoscopic sterilization is usually performed in the hospital under general anesthesia but can be performed under local anesthesia with conscious sedation. Overnight hospitalization for laparoscopy is rarely needed.

Open Laparoscopy

Standard laparoscopy carries with it a small but definite risk for injury to major blood vessels with insertion of the sharp trocar. With the alternative technique of open laparoscopy, neither

needle nor sharp trocar is used; instead, the peritoneal cavity is opened directly through an incision at the lower edge of the umbilicus (227). A special funnel-shaped sleeve, the Hasson cannula, is then inserted, and the laparoscope is introduced through it.

Techniques of Laparoscopic Sterilization

Sterilization is accomplished by any of four techniques: bipolar electrical coagulation, application of a small Silastic rubber band (Falope ring) (228), the plastic and metal Hulka clip (226), or the Filshie clip (229). The Filshie clip is new to the United States, although it has been used extensively in the United Kingdom and Canada (230). It is a hinged device made of titanium with a liner of silicone rubber tubing.

In the bipolar electrocoagulation technique, the midisthmic portion of the tube and adjacent mesosalpinx are grasped with special bipolar forceps, and radiofrequency electric current is applied to three adjacent areas, coagulating 3 cm of tube (Fig. 10.15). The tube alone is then recoagulated in the same places. The radiofrequency generator must deliver

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at least 25 watts into a 100-ohm resistance at the probe tips to ensure coagulation of the complete thickness of the fallopian tube and not just the outer layer; otherwise, the sterilization will fail (231).

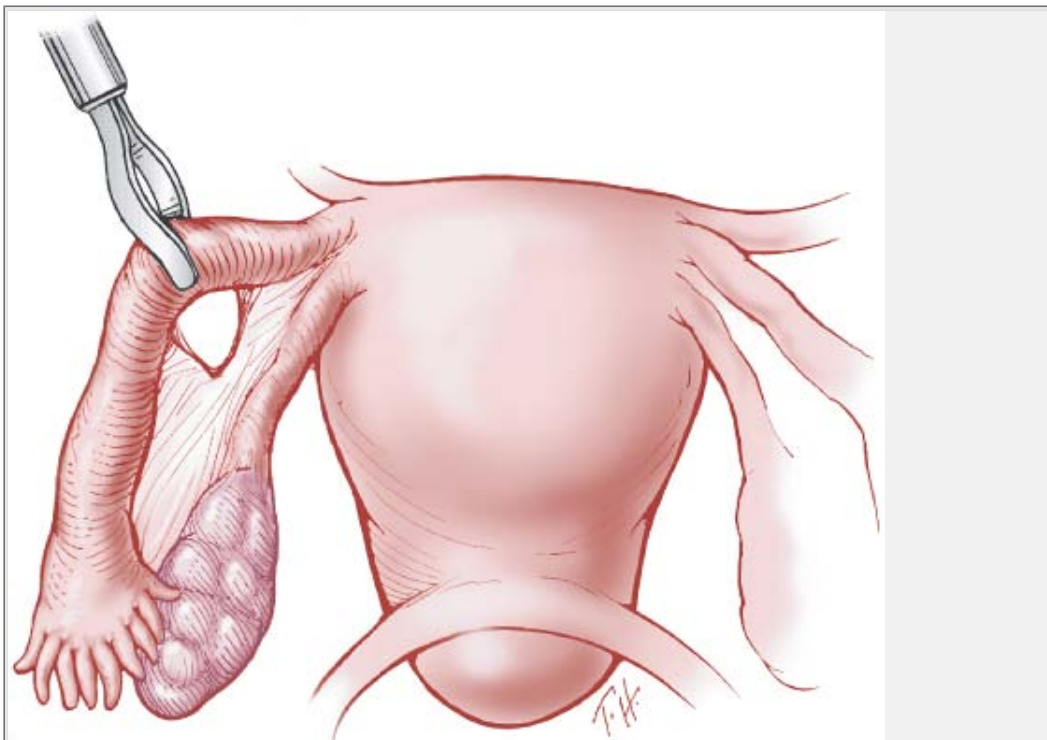


Figure 10.15 Technique for bipolar electrocoagulation tubal sterilization.

To apply the **Falope ring**, the midisthmic portion of the tube is grasped, with tongs advanced through a cylindrical probe that has the ring stretched around it. A loop of tube is pulled back into the probe, and the outer cylinder is advanced, releasing the Silastic ring around the base of the loop of tube, producing ischemic necrosis (Fig. 10.16). If the tube cannot be pulled easily into the applicator, the operator should stop and change to electrical coagulation rather than persist and risk lacerating the tube with the Falope ring applicator. The banded tube must be inspected at close range through the laparoscope to demonstrate that the full thickness of the tube has been pulled through the Falope ring.

The **Hulka clip** is also placed across the midisthmus, ensuring that the applicator is at right

angles to the tube and that the tube is completely contained within the clip before the clip is closed. The **Filshie clip** (Fig. 10.17) is also placed at right angles across the midisthmus, taking care that the anvil of the posterior jaw can be visualized through the mesosalpinx beyond the tube to ensure that the complete thickness of the tube is completely within the jaws of the clip before it is closed.

The electric and band or clip techniques each have advantages and disadvantages. Bipolar coagulation can be used with any fallopian tube. The Falope ring and Hulka and Filshie clips cannot be applied if the tube is thickened from previous salpingitis. There is more pain during the first several hours after Falope ring application. This can be prevented by bathing the tubes with a few milliliters of 2% lidocaine just before ring placement. Failures of the Falope ring or the clips generally result from misapplication, and pregnancy, if it occurs, is usually intrauterine. After bipolar sterilization, pregnancy may result from tuboperitoneal fistula and is ectopic in more than 50% of cases. If inadequate electrical energy is used, a thin band of fallopian tube remains that contains the intact lumen and allows intrauterine pregnancy to occur. Thermocoagulation, the use of heat probes rather than electrical current, is employed extensively in Germany for laparoscopic tubal sterilization but has had little use in the United States.

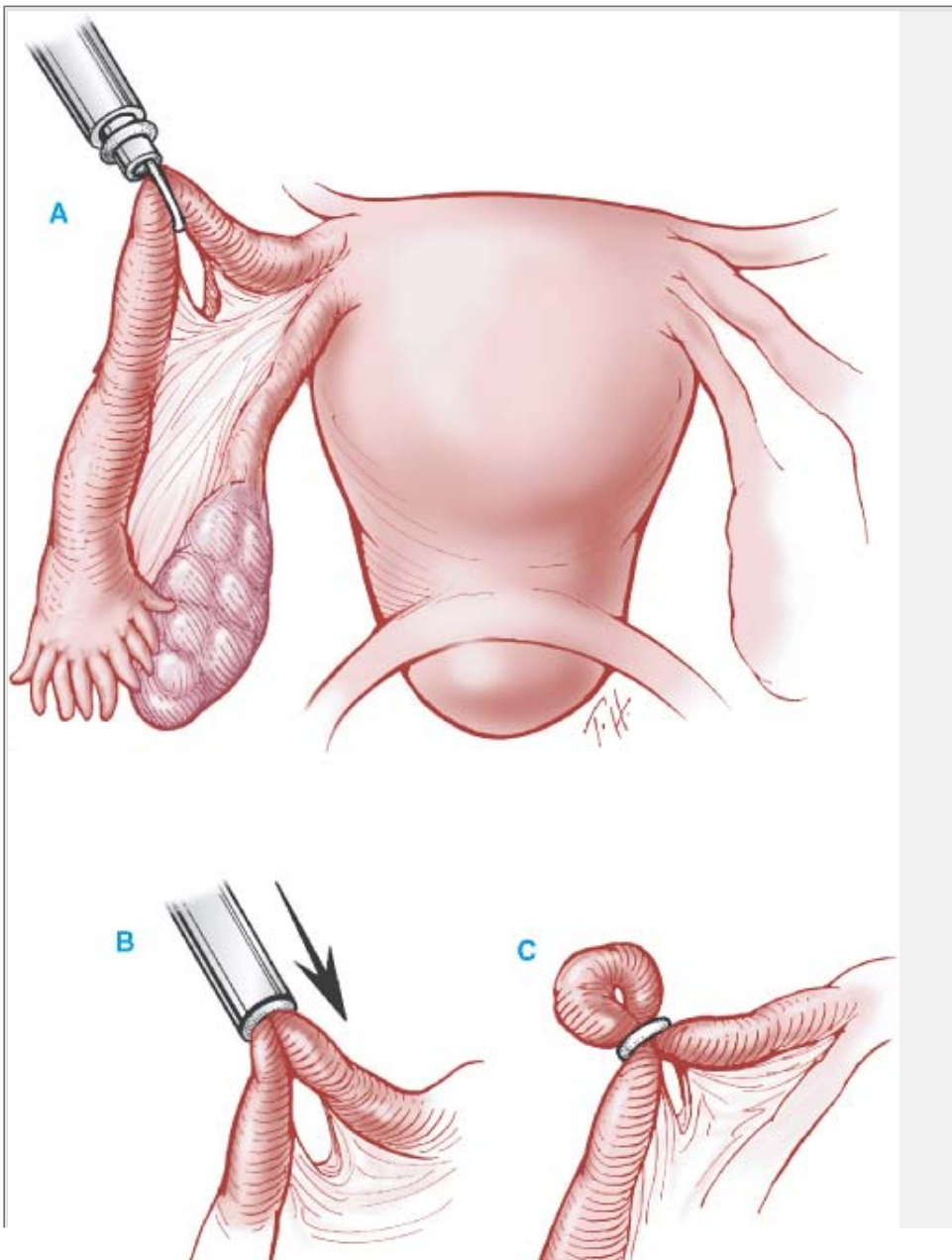




Figure 10.16 Placement of the Fallope ring for tubal sterilization.

Hysteroscopy

In 2002, the FDA approved a new hysteroscopic method of permanent birth control: the *Essure* system. *Essure* is a microinsert consisting of a soft stainless steel inner coil and a dynamic nickel titanium alloy outer coil (Fig. 10.18). The device is introduced into the uterus with a 5-mm operating channel hysteroscope and guided into the proximal section of the Fallopian tube at the uterotubal junction (Fig. 10.19). Over time, fibrous tissue grows into the device, occluding the tubes permanently. Placement of *Essure* can be performed under local anesthesia in an outpatient setting. No incision is needed. A non-steroidal antiinflammatory drug is given 1 to 2 hours before the procedure to decrease tubal spasm. The hysteroscope is introduced through the cervix, and the uterus is distended with saline. The tubal ostia are visualized. The *Essure* device is inserted through the operating channel of the hysteroscope on the end of a slender delivery wire and guided into the tubal opening and advanced into the tube. Once in place, an outer sheath is retracted, releasing the microinsert, which expands to anchor it in place. The delivery wire is detached and

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removed and the procedure repeated for the other tube. When properly placed, three to eight of the end coils of the microinsert are visible inside the uterus. The rest is inside the fallopian tube (232). Currently the FDA requires a 3-month follow-up x-ray hysterosalpingography examination to document tubal occlusion. The patient should continue to use contraception until this is demonstrated.



Figure 10.17 Filshie clip for tubal sterilization. (Courtesy of CooperSurgical, Inc., Trumbull, CT.)

Risks of Tubal Sterilization

Tubal sterilization is remarkably safe. In 1983, the total complication rate in a large series from several institutions was 1.7 per 100 (233). Complications were increased by use of general anesthesia, previous pelvic or abdominal surgery, history of PID, obesity, and diabetes mellitus. The most common significant complication was unintended laparotomy for sterilization after intraabdominal adhesions were found. In another series, 2,827 laparoscopic sterilizations were performed with the Silastic band using local anesthesia and intravenous sedation. Only four cases could not be completed (a technical failure rate of 0.14%), and laparotomy was not needed (234). Rarely, salpingitis can occur as a complication of the surgery. This occurs more often with electric coagulation than nonelectric techniques. From 1977 to 1981, there were 4 deaths per 100,000 procedures in the United States, less than the risk of one pregnancy; almost one half of the deaths were from complications of general anesthesia, usually related to the use of mask ventilation (235). The last

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U.S. national study was of sterilizations performed from 1979 to 1980. There were a total of 9 to 10 deaths per 100,000 sterilizations, but only 1 to 2 per 100,000 were attributed to the sterilization procedure alone (236). When general anesthesia is used for laparoscopy, endotracheal intubation is mandatory because the pneumoperitoneum increases the risk of aspiration. International data from the Association for Voluntary Surgical Contraception show a similar record of safety from third world programs: 4.7 deaths per 100,000 female sterilizations and 0.5 deaths per 100,000 vasectomies (237).



Figure 10.18 Essure device for hysteroscopic sterilization. (Courtesy of Conceptus, Inc.)

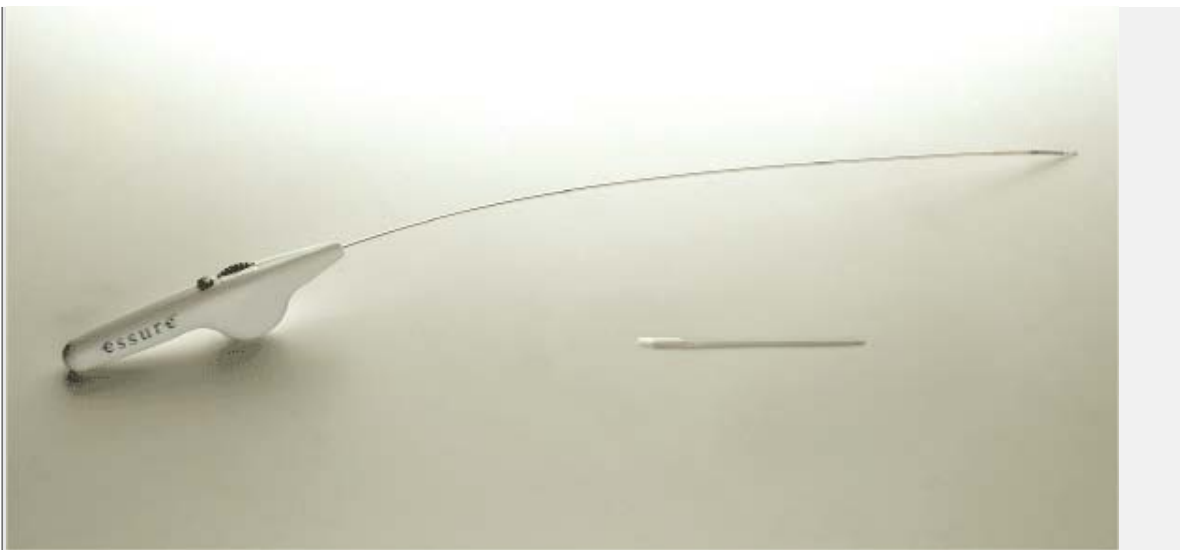


Figure 10.19 Essure device with guide wire and handle. (Courtesy of Conceptus, Inc.)

Family Health International has reported large randomized multicenter trials of the different means of tubal sterilization. The Filshie and Hulka clips were compared in two trials. A total of 2,126 women were studied, of which 878 had either clip placed by minilaparotomy and 1,248 had either clip placed by laparoscopy. The women were then evaluated at up to 24 months (238). **Pregnancy rates were 1.1 per 1,000 women with the Filshie clip and 6.9 per 1,000 with the Hulka clip at 12 months, a difference in rates that approached statistical significance** ($p = 0.06$). This same group compared the Filshie clip with the Silastic tubal ring in a similar study with a total of 2,746 women, of which 915 had the devices placed at minilaparotomy and 1,831 at laparoscopy (239). **Pregnancy rates at 12 months were the same for the Filshie clip and the tubal ring: 1.7 per 1,000 women.** The ring was judged more difficult to apply, but the Filshie clip was expelled spontaneously by three women during the 12 months of follow-up.

Possible but uncommon risks of the Essure system of hysteroscopic tubal sterilization include perforation of the device at insertion and expulsion of the device. There is theoretical risk of mutagenic or carcinogenic effect to the fetus from nickel alloy should pregnancy occur, although no such injury has been reported (232).

Benefits of Tubal Sterilization

In addition to providing excellent contraception, tubal ligation is associated with reduced risk for ovarian cancer that persists for as long as 20 years after surgery (240).

Sterilization Failure

Many "failures" occur during the first month after laparoscopy and are the result of a pregnancy already begun when the sterilization was performed. Contraception should be continued until the day of surgery, and a sensitive pregnancy test should be routinely performed on the day of surgery. Because implantation does not occur until 6 days after conception, however, a woman could conceive just before the procedure and

there would be no way to detect it. Scheduling sterilization early in the menstrual cycle obviates the problem but adds to the logistic difficulty. Another cause of failure is the presence of anatomic abnormalities, usually adhesions surrounding and obscuring one or both tubes. An experienced laparoscopic surgeon with appropriate instruments usually can lyse the adhesions, restore normal anatomic relations, and positively identify the tube. In

some circumstances, however, successful sterilization will not be possible by laparoscopy, and the surgeon must know before surgery whether the patient is prepared to undergo laparotomy, if necessary, to accomplish sterilization. Most studies of sterilization failure are short term.

The **Centers for Disease Control and Prevention's Collaborative Review of Sterilization (CREST)** reported on a cohort of 10,685 women sterilized from 1978 to 1986 at any of 16 participating centers in the United States who were followed from 8 to 14 years (241). The true failure rates for 10 years obtained by the life-table method are given in Table 10.9. Pregnancies resulting from sterilization during the luteal phase of the cycle in which the surgery was performed were excluded. Of all remaining pregnancies, 33% were ectopic. **The most effective methods at 10 years were unipolar coagulation at laparoscopy and postpartum partial salpingectomy, generally a modified Pomeroy procedure. Bipolar tubal coagulation and the Hulka-Clemens clip were least effective.** Younger women had higher risk for failure, as would be expected because of their greater fecundity.

Over the years since the CREST study began, sterilization by unipolar electrosurgery was abandoned because of the risk of bowel burns and was replaced with bipolar electrosurgery or the nonelectric methods (tubal ring, Hulka-Clemens clip, and more recently, the Filshie clip). An important later analysis of the CREST data found that bipolar sterilization could have a very low long-term failure rate if an adequate portion of the tube is coagulated. CREST study subjects who were sterilized with bipolar electrosurgery from 1985 to 1987 had lower failure rates than those sterilized earlier (1978–1985). **The important difference was in the technique of application of the electric energy to the tubes. Women whose bipolar procedure involved coagulation at three sites or more had low 5-year failure rates (3.2 per 1,000 procedures), whereas women who had fewer than three sites of tubal coagulation had a 5-year failure rate of 12.9 per 1,000 ($p = 0.01$) (242).**

In a large multicenter study, the Essure microinsert was successfully placed in 92% of the 707 women treated. Reasons for failure of insertion were tubal obstruction or stenosis or difficulty in accessing the tubal ostia. Correct placement was confirmed at 3 months in 96%, and complete bilateral occlusion occurred in 92%. Of those patients with complete occlusion, there were no pregnancies in 5,305 woman-months of use (243).

Table 10.9 Ten-year Life-table Cumulative Probability of Pregnancy per 1,000 Procedures with Different Methods of Tubal Sterilization, United States, 1978–1986

Unipolar coagulation	7.5
Postpartum partial salpingectomy	7.5
Silastic band (Falope or Yoon)	17.7
Interval partial salpingectomy	20.1
Bipolar coagulation	24.8
Hulka-Clemens clip	36.5
Total: all methods	18.5

From **Peterson HB, Xia Z, Hughes JM, et al.** The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. *Am J Obstet Gynecol* 1996;174:1164 (Table II), with permission.

Reversal of Sterilization

Reversal of sterilization is more successful after mechanical occlusion than after elec-trocoagulation because the latter method destroys much more of the tube.

With modern microsurgical techniques and an isthmus-to-isthmus anastomosis, pregnancy follows in about 75% of cases (244). A substantial risk for ectopic pregnancy exists after reversal. Hysteroscopic sterilization by the *Essure* procedure should be considered irreversible. Reversal has not been reported and would have to involve cornual resection and reimplantation of the fallopian tubes, a procedure with a very low success rate.

Late Sequelae of Tubal Sterilization

Increased menstrual irregularity and pain have been attributed to previous tubal sterilization. In patients who underwent the older laparoscopy technique with unipolar electrical destruction of a major portion of the tube, these concerns may be warranted (245). Study of the problem is complicated by the many women develop these symptoms even though they have not had tubal surgery and OCs reducing pain and creating an artificially normal menstrual cycle. Therefore, women who discontinued OC use concurrent with tubal sterilization will experience more dysmenorrhea, which is entirely unrelated to the sterilization. The best answer available also comes from the CREST study (246). A total of 9,514 women who had undergone tubal sterilization were compared with 573 women whose partners had undergone vasectomy. Both groups were followed up to 5 years with annual standardized telephone interviews. Women who had undergone tubal sterilization were no more likely to report persistent changes in intermenstrual bleeding or length of the menstrual cycle than women whose partners had vasectomy. The sterilized women, in fact, reported decreases in days of bleeding, amount of bleeding, and menstrual pain but were slightly more likely to report cycle irregularity (OR, 1.6; 95% CI, 1.1–2.3). Hence, **the CREST study found no evidence to support the existence of a post-tubal ligation syndrome.**

Vasectomy

Vasectomy, excision of a portion of the vas deferens, is readily accomplished with local anesthesia in an office setting. It does not decrease sexual performance (247).

The basic technique is to palpate the vas through the scrotum, grasp it with fingers or atraumatic forceps, make a small incision over the vas, and pull a loop of the vas into the incision. A small segment is removed, and then a needle electrode is used to coagulate the lumen of both ends. Improved techniques include the no-scalpel vasectomy, in which the pointed end of the forceps is used to puncture the skin over the vas. This small variation reduces the chance of bleeding and avoids the need to suture the incision. Another variation is the open-ended vasectomy, in which only the abdominal end of the severed vas is coagulated while the testicular end is left open. This is believed to prevent congestive epididymitis (248).

Reversibility

Vasectomy must be regarded as a permanent means of sterilization; however, with microsurgical techniques, vasovasostomy will result in pregnancy about one half the time. The longer the interval since vasectomy, the poorer is the chance of reversal.

Safety

Operative complications include scrotal hematomas, wound infection, and epididymitis, but serious sequelae are rare. There have been no reports of deaths from vasectomy in the United States in many years, and the death rate in a large third world series was only 0.5 per 100,000. Studies of vasectomized monkeys showed accelerated atherosclerosis, but several large-scale human studies have found no connection between vasectomy and vascular disease (249,250). Concerns about long-term safety recurred with the report of a possible association between prostate cancer and vasectomy (251). Prostate cancer is largely a disease of the western world and is strongly linked to dietary intake of animal fat,

family history, and race (252). In the west, it is more common in men of African American ancestry and rare in men of Asian descent. Recent studies are reassuring. A large, multiethnic, case control study from the United States and Canada compared 1,642 men with prostate cancer to 1,636 controls and found no overall association (OR, 1.1; 95% CI, 0.83–1.3) (253). A large case control study from Washington state reached the same conclusion (254). This study was especially important because of the high use of vasectomy in the community studied. Older reports may reflect bias, perhaps that higher-status men, with diets higher in animal fat, were more likely than lower-status men to choose vasectomy.

Abortion

Given the desire in developed countries to limit families to one or two children and the efficacy of contraception in general use, it is extremely likely that any normal couple will experience at least one unwanted pregnancy at some time during their reproductive years. In third world countries, desired family size is larger, but access to effective contraception is limited. As a result, abortion is common. Worldwide, about 46 million women have abortions each year, and about half of these procedures are illegal and considered "unsafe" by the World Health Organization definition: procedures carried out either by an unskilled person or in unsafe conditions, or both (255). **Where abortion is legal, it is generally reasonably safe; where it is illegal, complications are common, and about 78,000 women die every year from these complications** (255). Societies cannot prevent abortion, but they can determine whether it will be illegal and dangerous or legal and safe. Many countries in which abortion is completely illegal have very high rates of clandestine abortion. Abortion rates in representative countries are given in Table 10.10 (256).

Death from illegal abortion was once common in the United States. In the 1940s, more than 1,000 women died each year of complications from abortion (257). In 1972, 24 women died of complications of legal abortion and 39 died from known illegal abortions. In 2000, the last year for which complete data are available, there were 11 deaths from legally induced abortion, and no deaths from illegal abortion (abortion induced by a nonprofessional) in the entire United States (258). The American Medical Association's Council on Scientific Affairs has reviewed the impact of legal abortion and attributes the decline in deaths during this century to the introduction of antibiotics to treat sepsis; the widespread use of effective contraception beginning in the 1960s, which reduced the number of

unwanted pregnancies; and, more recently, the shift from illegal to legal abortion (259). The United States has a serious problem with teenage pregnancy. Without legal abortion, there would be almost twice as many teenage births each year.

Table 10.10 Rates of Induced Abortion in Representative Countries, 1985–1991 per 1,000 Women Aged 15–44 Years

Legal Abortion ^a		Illegal Abortion ^b	
Netherlands, 1986	5.3	Brazil, 1991	36.5
Canada, 1985	12.0	Columbia, 1989	32.7
England/Wales, 1987	14.2	Chile, 1990	45.4
United States, 1985	28.0	Mexico, 1990	22.3
Cuba, 1988	58.0	Peru, 1990	51.9
Former USSR, 1987	181.0	Dominican Republic	43.7

^a From **Henshaw SK, Morrow E.** Induced abortion: a world review. *Fam Plann Perspect* 1990;22:76–120, with permission.

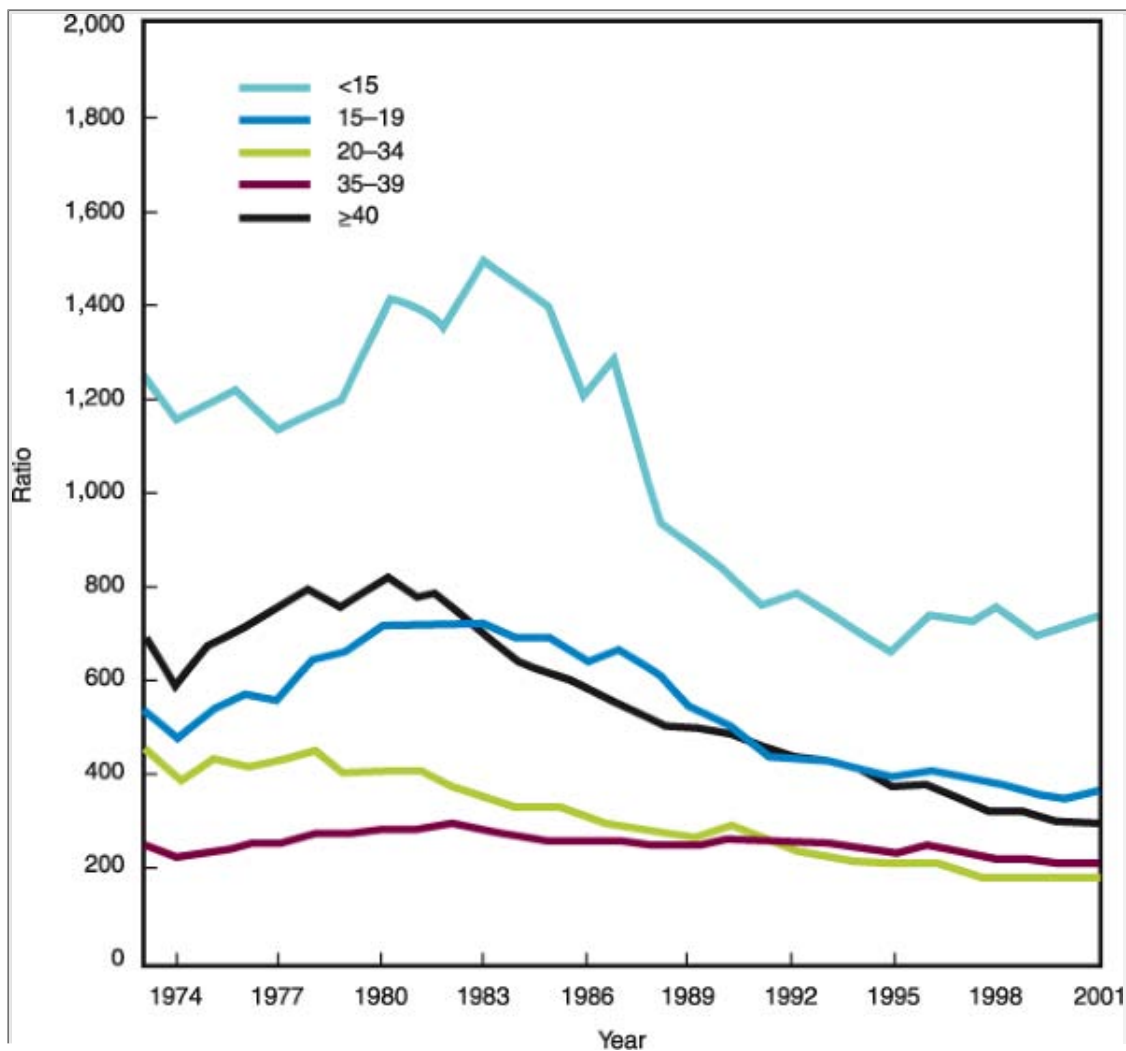
^b From **The Alan Guttmacher Institute.** *Aborto clandestino: Un realidad Latinoamericana.* New York, NY: The Alan Guttmacher Institute, 1994:24, with permission.

The number of abortions reported each year in the United States—1,313,000 in 2000 according to the Alan Guttmacher Institute—has been decreasing since the 1980s (260). In 2001, the national abortion ratio was 246 abortions for every 1,000 live births, and the national abortion rate was 16 per 1,000 women aged 15 to 44 years. Most women who obtain abortions are unmarried (82% in 2001), and the ratio of abortions to live births is 9 times higher for unmarried women than for married women (261). Use of abortion varies markedly with age. In 2001, 18% of women obtaining abortions were 19 years of age or younger, and 51.3% were 24 years of age or younger. In 2001, the abortion ratio for women younger than 15 years of age was 744 per 1,000 live births, almost as many abortions as births (Fig. 10.2). The lowest abortion ratio, 147 per 1,000 live births, is for women aged 30 to 34 years. Legal abortion rates and ratios reached their highest in the early 1980s as they replaced illegal abortions, and both have declined since, especially for the youngest women (Fig. 10.20) (258).

Regardless of personal feelings about the ethics of interrupting pregnancy, health professionals have a duty to know the medical facts about abortion and to share them

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with their patients (261). Providers are not required to perform abortions against their ethical principles, but they have a duty to help patients assess pregnancy risks and to make appropriate referrals.



<i>Procedure</i>	≤ 8	9–10	11–12	13–15	16–20	≥ 21
Vacuum curettage^b	0.3	0.7	1.1			
Dilation and evacuation				2.0	6.5	11.9
Instillation^c				3.8	7.9	10.3
Hysterectomy, hysterotomy	18.3	30.0	41.2	28.1	103.4	274.3

^a Legal induced abortion deaths per 100,000 legal induced abortions.

^b Includes all suction and sharp curettage procedures.

^c Includes all instillation methods (saline, prostaglandin).

From **Lawson HW, Frye A, Atrash HK, et al.** Abortion mortality, United States, 1972–1987. *Am J Obstet Gynecol* 1994;171:1365–1372, with permission.

Table 10.12 Complications of 170,000 First-Trimester Abortions

	Number of cases (%)	Rate
Minor complications		
Mild infection	784 (0.46)	1:216
Resuctioned day of surgery	307 (0.18)	1:553
Resuctioned subsequently	285 (0.17)	1:596
Cervical stenosis ^a	28 (0.016)	1:6,071
Cervical tear	18 (0.01)	1:9,444
Underestimation of gestational age	11 (0.006)	1:15,454
Convulsive seizure ^b	5 (0.004)	1:25,086
Total minor complications	1,483 (0.846)	1:118
Complications requiring hospitalization		
Incomplete abortion ^c	47 (0.28)	1:3,617
Sepsis ^d	36 (0.021)	1:4,722
Uterine perforation	16 (0.009)	1:10,625
Vaginal bleeding	12 (0.007)	1:14,166
Inability to complete abortion	6 (0.003)	1:28,333
Combined pregnancy ^e	4 (0.002)	1:42,500
Total requiring hospitalization	121 (0.071)	1:1,405

^aCausing amenorrhea.

^bAfter local anesthesia.

^cRequiring hospitalization.

^dTwo or more days of fever 40°C or higher.

^eIntrauterine and tubal pregnancy.

Adapted from: **Hakim-Elahi E, Tovel HM, Burnhill HM, Burnhill MS.** Complications of first trimester abortion: a report of 170,000 cases. *Obstet. Gynecol* 1990;76:129–135.

Complications of a large number of vacuum curettage procedures before 14 weeks of gestation from Planned Parenthood of New York City are presented in Table 10.12. Mild infection not requiring hospitalization and retained tissue or clot requiring resuctioning in the clinic were the most common complications. Somewhat fewer than 1% experienced any complication, and fewer than 1/1,000 were hospitalized (269). More extensive descriptions of the management of complications are published elsewhere (270,271).

Medical Means for First-trimester Abortion

Mifepristone (RU486), an analogue of the progestin *norethindrone*, has strong affinity for the progesterone receptor but acts as an antagonist, blocking the effect of natural progesterone. Given alone, the drug was moderately effective in causing abortion of early pregnancy; however, the combination of *mifepristone* with a low dose of *prostaglandin* proved very effective, producing complete abortion in 96% to 99% of cases (272). The FDA approved a protocol of *mifepristone*, 600 mg orally, followed 2 days later by *misoprostol*, 400 mg, also taken orally in women no more than 49 days from start of the last menstrual period. However, investigators have determined that 200 mg of *mifepristone* is as effective as 600 mg, and vaginal *misoprostol*, 800 µg, provides high efficacy within 63 days of amenorrhea (273,274). The *misoprostol* can be taken at 24, 48, or 72 hours after *mifepristone* with equal efficacy (275). Women may safely self-administer the *misoprostol* at home (276). **Contraindications to medical abortion with *mifepristone/misoprostol* include ectopic pregnancy; an IUD in place (remove IUD first); chronic adrenal failure;**

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concurrent long-term corticosteroid therapy; history of allergy to mifepristone, misoprostol, or other prostaglandin; and the inherited porphyries (277). The *mifepristone-misoprostol* combination has been studied for gestations at 9 to 13 weeks; although it is almost as effective as earlier in pregnancy, a larger proportion of patients will experience heavy bleeding and require vacuum curettage (278).

Methotrexate-Misoprostol and Misoprostol Alone

The antifolate *methotrexate* provides another medical approach to pregnancy termination but takes longer than the technique using *mifepristone/misoprostol* (279). Medical abortion can also be induced with *misoprostol* alone. Vaginal *misoprostol*, 800 µg, repeated in 24 hours if fetal expulsion has not occurred, produces a complete abortion in 91% of pregnancies up to 56 days of amenorrhea (280).

Complications of Medical Abortion

Heavy or prolonged bleeding is the principal complication, with up to 8% of women experiencing some bleeding for as long as 30 days (277). Need for surgical curettage is predicted by gestational age when the *mifepristone* is administered. Two percent of women treated at 49 days or less, 3% of those treated at 50 to 56 days, and 5% of those treated at 57 to 63 days needed curettage for bleeding or failed abortion in a large study with 200 mg of *mifepristone* and 800 µg of vaginal *misoprostol* (281). Late bleeding, at 3 to 5 weeks after expulsion of the pregnancy, accounted for more than half of the curettages. The complications reported to the manufacturer of *mifepristone* from the first 80,000 patients treated have been published (282). One woman died of ectopic pregnancy after refusing care. Another patient survived severe sepsis, and another, a 21-year-old woman with no risk factors, survived an acute myocardial infarction. Other severe sepsis cases have since occurred. A 27-year-old woman participating in a clinical trial in Canada died of multiple organ system failure from *Clostridium sordelli* sepsis after complete expulsion of a 5.5-week pregnancy despite receiving excellent care (283). Four other similar sepsis deaths have been reported in the popular press. **The five deaths in the United States occurred among approximately 500,000 women treated with *mifepristone/misoprostol*, allowing estimation of a case fatality rate of one per 100,000, comparable to the rate of death with surgical abortion and much less than the risk of childbirth (284).**

Second-trimester Abortion

Abortions performed after 13 weeks include those done because of fetal defects,

medical illness, or psychiatric problems that had not manifested earlier in pregnancy, and changed social circumstances, such as abandonment by the father. Young age is the single greatest factor determining the need for late abortion. In 2001, 25.8% of abortions in women younger than 15 years of age were midtrimester, whereas 16.9% of abortions for women 15 to 19 years of age and only 9.2% of abortions for women 30 to 34 years of age were performed after 12 weeks of gestation (258). These proportions have changed little in a decade.

Dilation and Evacuation

Dilation and evacuation (D&E) is the most commonly used method of midtrimester abortion in the United States. Typically, the cervix is prepared by insertion of hygroscopic dilators, stems of the seaweed *Laminaria japonicum* (laminaria). Placed in the cervical canal as small sticks, these devices take up water from the cervix and swell, triggering dilation. When the laminaria are removed the following day, sufficient cervical dilation is accomplished to allow insertion of strong forceps and a large-bore vacuum cannula to extract the fetus and placenta (285,286). Ultrasound guidance during the procedure is helpful (287). For more advanced procedures, laminaria are inserted sequentially over 2 or more days to achieve a greater degree of cervical dilation (288). At the end of the midtrimester, procedures

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that combine serial multiple laminaria dilation of the cervix with intrafetal injection of *digoxin*, induction of labor, and assisted expulsion of the fetus are used (289). Pretreatment with buccal *misoprostol*, 600 mg 2 to 4 hours before the procedure, is reported either to produce sufficient dilation to 14 mm or to permit easy forcible dilation to this diameter and is increasingly replacing laminaria in the early midtrimester (290).

Intact D&E is another modification useful for procedures at the end of the midtrimester. After wide cervical dilatation is achieved with multiple laminaria, the membranes are ruptured and an assisted breech delivery performed, with decompression of the after-coming fetal head to allow delivery of the fetus intact (291).

Labor-induction Methods

Intra-amniotic hypertonic saline or urea were widely employed techniques for labor induction abortion in the 1970s but have largely been supplanted by the use of synthetic prostaglandins.

Prostaglandins

Oxygenated metabolites of C₂₀ carboxylic acid, *prostaglandins* are found naturally in most biologic tissues, where they act as modulators of cell function. They act through specific receptors of the G-protein family that are coupled to a variety of intracellular signal mechanisms, which may stimulate or inhibit adenyl cyclase or phosphatidylinositol (292). Prostaglandins of the E and F series can cause uterine contraction at any stage of gestation. These agents can be given by intra-amniotic infusion, by intramuscular injection, or by vaginal suppository. The 15 methyl analogues of prostaglandin F_{2α} (*carboprost*) and prostaglandin E₂ (*dinoprostone*) are highly effective but frequently produce side effects of vomiting and diarrhea. *Misoprostol* is a 15 methyl analogue of PGE₁. A vaginal dose of 200 μg every 12 hours was shown to be as effective as *dinoprost* suppositories (20 mg every 3 hours) in patients with fetal death or intact pregnancy at 12 to 22 weeks of gestation (293). *Misoprostol*-treated patients experienced fewer side effects of fever, uterine pain, vomiting, and diarrhea. *Misoprostol* is much less expensive and easier to administer. In this study, patients with a living fetus were treated with ultrasound-guided intracardiac injection of potassium chloride to ensure fetal death before administration of *misoprostol*. A comparison of 200-, 400-, and 600-μg doses

of misoprostol at 12-hour intervals produced rates of abortion of 70.6%, 82%, and 96%, respectively, within 48 hours; however, the side effects of vomiting, diarrhea, and fever increased with increasing doses (294). In a comparison of three dosing regimens, 400 µg of *misoprostol* vaginally every 6 hours was optimal for efficacy without increasing side effects (295). Uterine rupture has been reported in three women with previous cesarean delivery treated with *misoprostol* in the midtrimester, but in a case series of 101 women with one or more previous cesarean births and three smaller case series totaling 87 patients, no ruptures occurred (296). Larger series are needed to quantify the risk.

Transient fetal survival is not infrequent after prostaglandin inductions. In the United States, it is common to produce fetal demise before induction. Intra-amniotic *digoxin*, 1 to 1.5 mg, or fetal intracardiac *potassium chloride* (3 mL of a 2-mmol solution) are commonly used for this purpose. Induction of fetal death with intracardiac administration of potassium chloride also has been shown to shorten the interval to fetal expulsion when abortion is induced with vaginal *dinoprostone*, and it is likely the same effect would occur with *misoprostol* induction (297).

Retained placenta is another common problem of abortions in which labor is induced. Rectal administration of 800 µg of *misoprostol* has been reported to produce prompt placental expulsion (298).

Midtrimester Mifepristone/Misoprostol

***Mifepristone* pretreatment markedly increases the abortifacient efficacy of both *gemeprost* and *misoprostol*.** The mean interval from start of the prostaglandin to fetal expulsion is reduced to 7 to 9 hours, much

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shorter than with the prostaglandin alone (299). *Mifepristone*, 200 mg, is just as effective for this purpose as 600 mg (300).

High-dose Oxytocin

***Oxytocin* in very high doses is as effective as *dinoprostone* at 17 to 24 weeks of pregnancy** (301). Patients initially receive an infusion of 50 units of *oxytocin* in 500 mL of 5% dextrose and normal saline over 3 hours; 1 hour of no *oxytocin*, followed by a 100-unit, 500-mL solution over 3 hours; another hour of rest; and then a 150-unit, 500-mL solution over 3 hours, alternating 3 hours of *oxytocin* with 1 hour of rest. The *oxytocin* is increased by 50 units in each successive period until a final concentration of 300 units per 500 mL has been reached.

Complications

The labor-induction methods share common hazards: failure of the primary procedure to produce abortion within a reasonable time, incomplete abortion, retained placenta, hemorrhage, infection, and embolic phenomena. Failed abortion can lead to serious infection and continued blood loss. If fetal expulsion has not occurred within 24 to 36 hours, consideration should be given to a D&E procedure.

Selective Reduction

Multifetal pregnancies are at risk for extremely preterm birth and major neonatal complications. To prevent this, selective reduction of higher-order multiple gestations often is practiced. The largest series describes 3,513 pregnancies treated with ultrasound-guided fetal intracardiac injection of potassium chloride (0.2–0.4 mL of a 2-mmol solution in the first trimester, 0.5–3.0 mL in the second trimester). The rate of fetal loss fell as operators gained experience. Loss was higher with higher starting number of

gestations (starting number greater than six, 15.4% loss, decreasing to 6.2% loss for starting number of two gestations), and also higher if more fetuses were left intact (finishing number three, 18.4% loss, decreasing to 7.6% for finishing number of gestations of one) (302). Another indication for selective reduction is the presence of one anomalous fetus in a multifetal gestation. In a series of 402 patients treated for this indication, rates of pregnancy loss after the procedure by gestational age at the time of procedure were 5.4% at 9 to 12 weeks, 8.7% at 13 to 18 weeks, 6.8% at 19 to 24 weeks, and 9.1% at 25 weeks or more (303). No maternal coagulopathy occurred, and no ischemic damages or coagulopathies were seen in the surviving neonates. **Selective reduction should not be attempted with monoamniotic twins or with twin-twin transfusion syndrome because of the possibility of embolic phenomena and infarction in the surviving twin.** Maternal serum α -fetoprotein remains elevated into the second trimester after first-trimester procedures.

The Future

Spermicides

Synthetic analogues of *zidovudine* have been found to be nontoxic in the reproductive tracts of rabbits and monkeys. These agents markedly reduce the ability of sperm to fertilize oocytes, and they have potent anti-HIV activity in HIV replication assays (304). Several novel nonnucleoside inhibitors have been synthesized that also are spermicides with high anti-HIV activity under laboratory conditions.

Intrauterine Devices

The *GyneFix*, a frameless copper IUD now available in Europe, consists of a surgical suture with small copper cylinders crimped to it. The knot on the proximal end of the suture is pushed 1 cm into the uterine wall with a special inserter. Comparative trials have found it more effective than the *copper T380A* and to have fewer instances of expulsion and to require removal for pain and bleeding less often (305). It is of considerable interest for these reasons as well as for its excellent retention after postabortal insertion.

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Vaginal Rings

Silastic vaginal rings releasing either progestin or progestin-estrogen combinations have been studied for years and are now undergoing field trials in a number of countries. The presently available *NuvaRing* contains both estrogen and progestin and has the same safety concerns as the other estrogen-containing hormonal methods. Interest continues in development of a progestin-only ring for high contraceptive efficacy without estrogen (82).

Simple Means for Female Sterilization

Another critical area for contraceptive development is a nonsurgical means of sterilization of both men and women. Intrauterine quinine is the most promising method for nonsurgical female sterilization, but the method is embroiled in controversy because it was largely developed in the third world and moved quickly to widespread use without adequate proof of safety (306). The technique is very simple: Pellets containing 252 mg of *quinacrine* are inserted into the uterus through an IUD inserter during the proliferative phase of the cycle and again 1 month later. Intrauterine quinine produces sclerosis of the proximal fallopian tube. In a large trial in Vietnam, the 1-year pregnancy rate for 9,461 women who received 2 doses was 2.63 per 100 woman-years. The rate of ectopic pregnancy was 0.89 per 1,000 woman-years (307). A subsequent study with 2,551,355 woman-years of exposure found the rate of ectopic pregnancy

to be 0.26 per 1,000 women treated with *quinine*, which was similar to surgical sterilization and the IUD, OC pills, and condoms (0.42–0.45 per 1,000) and less than nonusers of contraception (1.18 per 1,000) (308). Ongoing studies in developed countries will hopefully replicate these results (306).

Contraceptive Vaccines

Immunologic contraception—sterilization with vaccination against human chorionic gonadotropin was pursued for many years in India but appears to have been abandoned (309). Zona pellucida glycoproteins are another target for a potential vaccine, but application in humans appears blocked by the ovarian dysfunction observed in animal studies (310). The search continues for target proteins unique to reproduction to which a vaccine could be employed without adversely effecting other functions.

Male Contraception

As described earlier, considerable progress has been made in hormonal contraception for men based on long-acting androgens and androgen–progestin combinations. Nonhormonal male methods are being investigated. These include efforts to target and specifically interfere with spermatogenesis, epididymal sperm maturation, and sperm function (311).

Chinese researchers have developed a method of percutaneous occlusion of the vas that was used in more than 100,000 men; it is effective and appears to be reversible. *Polyurethane elastomer* is injected into the vas, where it solidifies and forms a plug, providing an effective block to sperm. The plugs are removed using local anesthesia, and fertility returns in most cases after as long as 4 years with the plugs in situ (312).

Gossypol, an extract of cottonseed, was evaluated in China as a male contraceptive but abandoned because of problems with hypokalemia in users. More recently there has been an explosion in research in *gossypol* chemistry and biology because of its potential as an antineoplastic agent. It is being used successfully for contraception seemingly without complications in China in a purified form at reduced doses (313). A multinational study also found hypokalemia not to be a problem. Of 151 men treated, 65% had sperm counts fewer than 1 million/mL. About half of men followed more than 1 year after treatment reverted to a normal sperm count. *Gossypol* may become an alternative to vasectomy (314).

Perhaps the most important current area of contraceptive research is the development of nontoxic spermicides that would also prevent HIV transmission and nonsurgical means for male and female sterilization (305).

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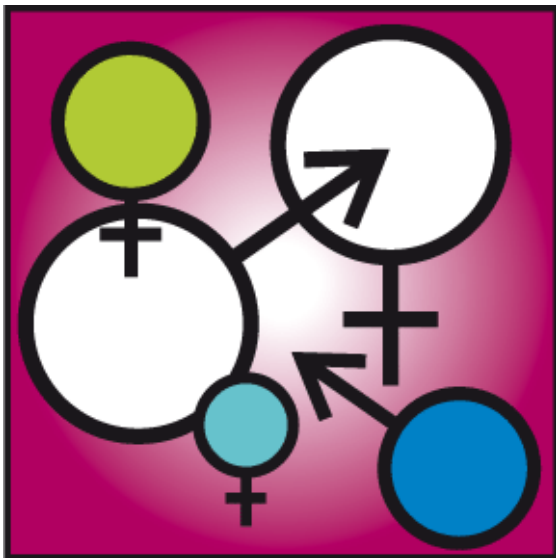
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11

Sexuality, Sexual Dysfunction, and Sexual Assault

David A. Baram

Rosemary Basson



- **Most young men and young women have multiple serial sexual partners but use condoms inconsistently, thereby exposing themselves to sexually transmitted diseases (STDs) and unintended pregnancies.**
- **Sexual response is mediated by a complex interplay of psychological, interpersonal, environmental, and biological (hormonal, vascular, muscular, neurological) factors.**
- **Numerous factors can affect sexual response, including age; relationship duration and quality; personal psychological factors stemming from relationships in childhood with parental figures; previous losses, traumas, and ways of coping with emotions generally; illness; and use of medication, alcohol, and illicit drugs.**
- **Physical, emotional, and economic stressors of pregnancy may negatively affect emotional and sexual intimacy. Sexual attitudes and behavior during pregnancy and postpartum are influenced by sexual value systems,**

folklore, religious beliefs, physical changes, and medical restrictions.

- Despite the importance of issues relating to sexuality, many women may find it difficult to talk to their physicians about sexual concerns, and many physicians are uncomfortable discussing sexual issues with their patients.

- Asking about sexual concerns gives physicians an opportunity to educate patients about the risk of STDs, encourage safer sex practices, evaluate the need for contraception, dispel sexual misconceptions, and identify sexual dysfunction.

- Many of the sexual problems couples encounter are due to a deficit of knowledge or experience, sexual misconceptions, or inability of the couple to communicate about their sexual preferences.

- Sexual problems are common in the general population in the United States. Vaginismus is an involuntary reflex precipitated by real or imagined attempts

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at vaginal entry. Dyspareunia may affect two thirds of women during their lifetime.

- Sexual assault of children and adult women has reached epidemic proportions in the United States and is the fastest growing, most frequently committed, and most underreported crime. The terms *sexual abuse survivor* and *assault survivor* are preferable to *victim*.

- Childhood sexual abuse has a profound and potentially lifelong effect on the survivor. Although most cases of childhood sexual abuse are not reported by the survivor or her family, it is estimated that as many as one third of adult women were sexually abused as children.

- Women who have been sexually abused as children or sexually assaulted as adults often experience sexual dysfunction and difficulty with intimate relationships and parenting.

- The National Women's Study revealed that 13%, or one of eight adult women, are survivors of at least one completed rape during their lifetime.

Most women feel that sexuality is an important part of their lives. Providing patients with information about normal sexual changes that occur with puberty, pregnancy and postpartum, menopause, and older age is part of routine obstetric and gynecologic care. Sexual dysfunction can arise from gynecologic diseases such as endometriosis, procedures such as those associated with infertility, and treatments such as pelvic radiation, bilateral salpingo-oophorectomy, and use of gonadotropin-releasing hormone antagonists (1,2,3,4,5,6). Sexual abuse can have long-lasting effects on sexuality as well as other psychophysiological aspects of a patient's life (3). Inquiry about sexual concerns and explanation of the implications of a disease and its treatment are integral components

of gynecologic care.

Sexuality

The spectrum of normal sexual response varies from one woman to another and throughout a woman's lifetime (4,5). Physicians should be aware of their patients' sexual values, attitudes about specific practices, and concerns about their sexuality. Maintaining open communication with patients about their sexuality allows the physician to counsel them about sexual issues and problems as well as other aspects of their reproductive health.

Sexual Practices

Sexual activity among adolescents in the United States has increased during the past 20 years (3). The average age for first intercourse for both men and women is 16 years. By 19 years of age, as many as three quarters of women will have had intercourse. Most young men and young women have multiple serial sexual partners but use condoms inconsistently, thereby exposing themselves to STDs and unintended pregnancies. A survey of men and women between the ages of 18 and 59 in the United States reported that most men and women were satisfied with their sexual lives even if sex was infrequent (4). Approximately 47% of women had sexual activity with their partners a few times each month, 31% estimated they had sexual activity 2 to 3 times a week, and 7% more than 4 times a week. Twelve percent of women had sex a few times a year, and approximately 3% had never been sexually active. Most men and women stated they were monogamous. Of those who were married, 85% and 75% of women and men, respectively, said they have never been unfaithful. Homosexual activity in the previous year was reported by 3% of women and 2.7% of men and at some time in the past by 3.8% of women and 7.1% of men. Although 22% of women said they had been forced to do something sexual, usually by someone they loved, only 3% of men admitted to forcing themselves sexually on a woman.

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Sexual Physiology

For most women, their clitoral tissue is the most sexually sensitive part of their anatomy, and its stimulation produces the most intense sexual feelings and the most intense orgasms. However, many women first need to experience nonphysical and nongenital physical stimulation before clitoral stimulation can be enjoyed. In the absence of arousal, direct clitoral stimulation can be unpleasant and be perceived as too intense and even painful. Recent immunohistologic studies have identified neurotransmitters thought to be associated with sensation concentrated right under the epithelium of the glans clitoris (1). Clitoral tissue extends far beyond the visible portion when the clitoral hood is retracted. It includes the clitoral head, shaft, rami running along the pubic arch, periurethral tissue in front of the anterior vaginal wall, and the bulbar tissue under the superficial perineal muscles surrounding the anterior distal vagina. Other sexually sensitive areas include the nipples, breasts, labia, much of the skin generally, and to some extent, the vagina. Although the lower third of the vagina is responsive to touch, the upper two thirds are sensitive primarily to pressure. The rich supply of nerves in the fascia anterior to the upper vagina (Halban's fascia) and the proximity of the clitoral type of spongy tissue around the urethra anterior to the vagina contribute to the pleasurable sensations of intercourse. However, many women experience orgasm more easily from direct clitoral touch, possibly provided at the same time as intercourse.

There has been speculation about the existence of a "G-spot," named after Ernest Gräfenberg, who had first described it in 1944 (1,2). This area of the vagina, located anteriorly midway between the symphysis pubis and cervix, is thought to be exquisitely sensitive to deep pressure. Stimulation of this area has been associated with orgasm and loss of fluid that has not been scientifically proven to be anything other than dilute urine. Women who are normally continent often leak urine at orgasm; this is not abnormal and does not require medical intervention.

Sexual Response Cycle

Sexual response is mediated by a complex interplay of psychological, interpersonal, environmental, and biological (hormonal, vascular, muscular, neurological) factors. The initial phase of the sexual response cycle may be one of desire, but more often women, particularly those in long-term relationships, are motivated by factors other than sexual desire (2,3,4,5,6). Women initiate or consent to sex for many reasons, including a desire to increase emotional intimacy with their partners. By directing her attention to sexual stimulation, a woman's subjective sexual arousal/pleasure/excitement triggers sexual desire. Desire and arousal coexist and compound each other (Fig. 11.1). Sexual satisfaction (with one,

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or many, or no orgasms) can be achieved if a woman can stay focused, her pleasure continues, the duration of the stimulation is sufficiently long, and there is no negative outcome (e.g., pain or partner dysfunction). The response is circular, with phases overlapping and in variable order (e.g., desire may follow arousal, and higher arousal may follow the first orgasm). Desire, once triggered, increases the motivation to respond to sexual stimuli and to agree to or ask for more intensely erotic forms of stimulation. **Any initial spontaneous desire will augment the response.**

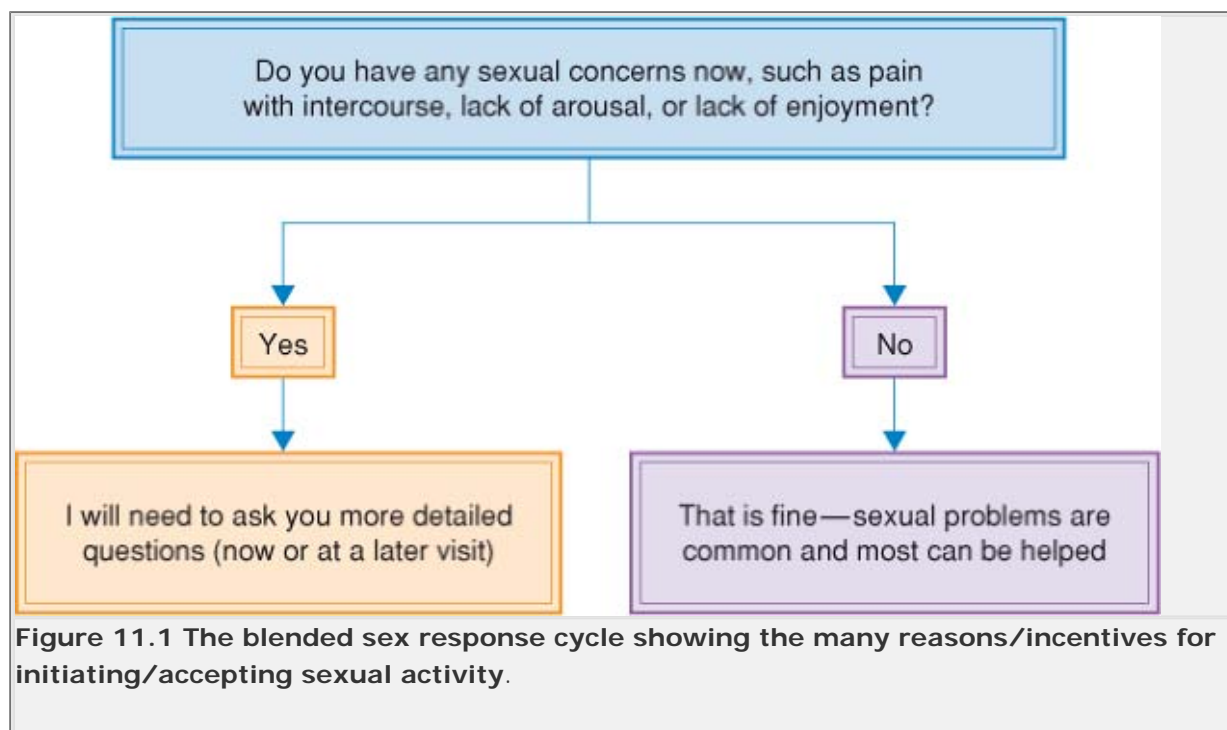


Figure 11.1 The blended sex response cycle showing the many reasons/incentives for initiating/accepting sexual activity.

Desire and Arousability

Sexual desire provides strong motivation to be sexual. Feelings of desire may be triggered by both internal (e.g., fantasies, memories, feelings of arousal) and external (e.g., an interested and interesting partner) sexual cues and are dependent on adequate neuroendocrine function (5). Multiple neurotransmitters, peptides, and hormones modulate desire and subjective arousal. Substances that promote sexual response include norepinephrine, dopamine, oxytocin, and serotonin. Prolactin and GABA inhibit sexual response. These peptides and neurotransmitters are themselves modulated by sex hormones. However, it is clear that biological factors do not act independently from environmental factors, a finding in human as well as animal models. Dopamine and progesterone, acting on receptors in the hypothalamus, both cause an increase in sexual behavior in female rats that have undergone oophorectomy and received estrogen. However, the presence of a male animal in an adjacent cage can cause an identical change in sexual behavior (7). Likewise, the ability to be aroused and intensity of response can be increased in women by giving them a modest dose of testosterone, by administering *bupropion* (dopaminergic), or by a change of partner (8,9). Even in rodents, complex networks exist whereby the female assesses the context of potential sexual activity and relates it to past experience and, therefore, expectation of reward (10). In women, sexual interest is influenced by their psychological mindset, beliefs and values, expectations, sexual orientation, preferences, and the presence of a safe and erotic environmental setting. Sexual desire, interest, and arousability are most strongly influenced by mental health and feelings for the partner, both generally and specifically, at the time of sexual interaction (11,12,13). Sexual desire also is strongly influenced by fatigue; as a result, sex late at night is not usually attractive to a busy woman. Similarly, chronic illness typically reduces desire and arousability.

Sexual Arousal

Accompanying the subjective excitement and erotic feelings of arousal are a number of physical changes. These changes include genital swelling; increased vaginal lubrication; engorgement of the breasts and nipple erection; increases in skin sensitivity to sexual stimulation; changes in heart rate, blood pressure, muscle tone, breathing, body temperature; mottling of the skin; and a "sex flush" of vasodilation over the chest, breasts, and face. With sexual stimulation, brain activity in the hypothalamus and other areas influencing the genital response are activated, triggering the autonomic nervous system to allow increased blood flow to the vagina. Vasodilation of the arterioles in the submucosal vaginal plexus increases transudation of interstitial fluid, which moves from capillaries between the epithelial intercellular spaces and into the vaginal lumen. Simultaneously, the autonomic nervous system allows relaxation of the smooth muscle cells surrounding blood spaces (sinusoids) in the clitoris and labia, causing clitoral swelling and vasodilation in the labia. Recent immunohistologic studies indicate nerves containing nitric oxide are present in the genital skin covering the clitoris and labia (1).

With arousal, the vagina lengthens, distends, and dilates, and the uterus elevates out of the pelvis. With increased sexual stimulation, vasocongestion reaches a maximum intensity. Genitally, the labia become more swollen and darker red and the lower third of the vagina swells and thickens to form an "orgasmic platform." The clitoris becomes more swollen and elevates to a position near the symphysis pubis, and the uterus elevates fully

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out of the pelvis. The breasts become more engorged, the skin more mottled, and the nipples more erect.

The neurobiology of arousal is incompletely understood but the genital vasocongestive responses appear to be highly automated, occurring within seconds of an erotic stimulus (14). Parasympathetic nerves release nitrous oxide and

vasointestinal polypeptide (VIP), mediating vasodilation (12,15). Acetylcholine (ACh) blocks noradrenergic vasoconstrictive mechanisms and promotes nitrous oxide release from endothelium. The parasympathetic and sympathetic nervous systems and the somatic system function less independently than was previously believed. Communication has been identified between the cavernous nerves to the clitoris containing nitrous oxide and the distal portion of the (somatic) dorsal nerve of the clitoris from the pudendal nerve (1). The pelvic sympathetic nerves primarily release (vasoconstrictive) noradrenaline and adenosine triphosphate, but some release ACh, nitrous oxide, and VIP. Nitric oxide is thought to be the major neurotransmitter involved in vulvar engorgement (1,15). In the vagina, VIP, nitrous oxide, and other unidentified neurotransmitters are involved (15).

Even in women without any sexual dysfunction, there is highly variable correlation between the degree of subjective sexual excitement and the increase in congestion around the vagina (14,16). This correlation has been shown repeatedly over the past 25 years based on psychophysiologic studies using a tamponlike photoelectric device placed in the vagina while the woman views an erotic video. Congestion in response to the sexual video is reduced in women with disruption of the autonomic nerve supplying the vulva and vagina (e.g., from non-nerve-sparing radical hysterectomy). However, otherwise healthy women experiencing chronic lack of arousal (including lack of subjective excitement and lack of any awareness of genital congestion), show increases in vaginal congestion from erotic stimuli that are similar those in control women (14,17). With the so-called cervico-motor reflex, cervical touch (in the laboratory with a balloon-tipped catheter, which might be replicated by penile pressure) leads to a reduction in pressure in the upper portion of the vagina and an increase in pressure in the middle and lower portions. Simultaneously, an increase in electromyographic activity in the levator ani and puborectalis muscles was recorded. It is thought that during intercourse penile thrusting on the cervix might cause contraction of the pelvic muscles to facilitate "ballooning" of the upper vagina, perhaps to facilitate pooling of semen. The same muscle contraction constricts the lower vagina, which may afford increased stimulation of the partner's penis, thereby maintaining rigidity (18).

A further reflex demonstrated in laboratory studies shows reduced uterine tone in response to mechanical or electrical stimulation of the glans of the clitoris. Background activity of the uterine muscle was abolished by clitoral stimulation if either the glans clitoris or the uterus was anesthetized. Uterine pressure declined on clitoral stimulation. **This reflex may underlie the known increase in size and the elevation of the uterus with sexual arousal** (19).

Orgasm

Orgasm is described as the most intensely pleasurable of the sexual sensations. It involves a myotonic response of smooth and striated muscle associated with feelings of sudden release of the sexual tension built up during arousal. Reflex rhythmic contractions (3–20 0.8/sec) of the muscles surrounding the vagina and anus occur. Uterine contractions also are experienced by many women during orgasm, who may perceive a difference in their orgasms after hysterectomy. The majority of women most easily experience orgasm from direct clitoral stimulation. More direct contact with the clitoris is possible from contact of pubis to pubis after the man has ejaculated and penile size is reduced. The bodies are more closely approximated and the woman can move her pelvis on his at a rate that is most conducive to her orgasm. Breast stimulation, kissing and clitoral stimulation during intercourse are other common means of experiencing orgasm. Women are potentially

multiorgasmic, capable of experiencing a number of orgasms close together during one sex response cycle and of resuming sexual activity without any refractory period.

Resolution

Following the sudden release of sexual tension brought about by orgasm, women experience a feeling of relaxation and well-being. The gradual lessening of pelvic engorgement contrasts with the quicker loss of penile firmness in men. Nongenital changes that took place during arousal are reversed, and the body returns to a resting state after some 5 to 10 minutes. With further stimulation, however, the response can resume. Women who enjoy arousal without orgasm and without any sense that orgasm is very close but frustratingly absent report a similar sense of well-being and relaxation.

Recent research has indicated that these phases of sexual response are not discrete entities in an invariable order, as was originally described by Masters and Johnson and Kaplan, but rather circular in nature. They differ from one woman to another and can be affected by a variety of factors.

Factors Affecting Sexual Response

Numerous factors can affect sexual response (20,21,22,23). They include age; relationship duration and quality; personal psychological factors stemming from relationships in childhood with parental figures; previous losses, traumas, and ways of coping with emotions generally; illness; and use of medication, alcohol, and illicit drugs.

Mental Health

Lack of emotional well-being was one of the stronger predictors of sexual distress in the North American National Probability Sample (24). It has also been shown that lack of mental well-being, even if it does not meet the criteria of a clinical diagnosis of mental disorder, is strongly linked to women's symptoms of low desire (25). One study showed a strong association between decreased sexual interest and self-reporting of negative emotional and psychological feelings, including low self-esteem, feelings of insecurity, and lost femininity (25). Impaired sexual desire has been noted in most studies of women with depression, even before the administration of antidepressants with sexually negative side effects (26). Paradoxically, depressed women may masturbate more frequently than women who are not depressed despite an increased prevalence of dyspareunia and difficulties with arousal and orgasm (27).

Aging

The degree to which aging and the marked changes in ovarian function associated with menopause may affect women's sexual response has recently been addressed in large population studies. **Some studies have shown little increase in sexual problems with age (3), whereas in others almost 40% of the sample reported reductions in responsiveness and an increased desire for nongenital sexual expression (20,28).** In one study, the prevalence of reduced desire increased significantly as a function of both menopause status and age, from 22% in the premenopausal group to 32% in the postmenopausal group (29). Low levels of desire were strongly associated with other sexual problems, including difficulties with arousal and orgasm. One large cohort of women studied over 10 years from peri- to postmenopause showed a decline in desire and responsiveness as a function of both age and menopause (13). The independent effect of menopause, however, was indirect. The number of menopausal symptoms experienced influenced well-being, which in turn affected sexual responsiveness and sexual desire and interest.

Many studies of sexuality and aging show that older women report less distress about lack of desire when compared with younger women (11,24,30). In a nonclinical study of 102 women, the determinants of sexual satisfaction in those younger than 45 years of

age were compared with those of women older than 45 years of age (11). There was no difference in sexual satisfaction achieved either by intercourse or noncoital sexual activities. However, older women reported lower frequency of orgasm and different ratings on certain dimensions of sexual satisfaction. For the older women, the dominant qualities important to their satisfaction were those related to an emotional sense of calm and to factors such as feeling secure with their partner, whereas for younger women the subjective physical experience was more important.

Despite reports of reduced sexual interest and desire by some women, most retain some interest and maintain the potential for sexual pleasure for their entire lives. In older women, a strong predictor of continued sexual interest is sexual behavior and enjoyment at an earlier age. A discrepancy between sexual interest and actual sexual activity occurs in many cases because an adequate partner is no longer available. In other instances, the cessation of sexual activity with age is more an expression of emotional problems resulting from lack of tenderness, communication, and attraction.

In addition to partner availability, an older women's sexuality is influenced by her partner's general and sexual health (31,32) and the relationship itself, which will determine how well the couple can adapt to changes in their sexual function as they age. Although some older women may retain negative societal attitudes to sex that is not "natural" (i.e., not intercourse oriented), studies have shown a shift from genital sex to intimacy as people age, indicating that any activity that involves affection, romance, intimacy, and companionship may help satisfy the sexual needs of older adults (33). Whether this will change with the evolution of safe and more effective medications for treating erectile dysfunction remains to be seen. For some older women, it is clear that the setting, whether nursing home or grown-up child's home, will be important factor in realizing sexual goals.

If intercourse is perceived as a necessary component of sexual activity with a partner, some older women will lose motivation and interest as a result of discomfort and dyspareunia associated with lack of estrogen. Although the increase in vaginal congestion in response to visual sexual stimulation has been shown to be similar in women with and without estrogen, baseline vaginal blood flow is lower in estrogen-deficient women (14,34). Thus, the increase in lubrication may be insufficient. Also, there may be loss of elasticity and thinning of the vaginal epithelium, which becomes vulnerable to damage from intercourse. Estrogen depletion predisposes women to vulvar vaginitis and urinary tract infections, both of which contribute to dyspareunia and reduce sexual self-image. Women who remain sexually active, alone or with a partner, have less vulvar and vaginal atrophy than inactive women.

Adrenal production of testosterone precursors gradually decreases with age, beginning in the late 30s. Recent attempts to correlate testosterone levels with sexual function or dysfunction in premenopausal women are conflicting, and there is even less clarity regarding postmenopausal women (35,36). **In surgically menopausal women, testosterone supplementation, given in combination with estrogen at levels equal to or only slightly above premenopausal values, has been shown to improve arousal, sexual responsiveness, orgasmic intensity and frequency, and desire (8,37).** Older studies used pharmacological doses of testosterone. The whole question of supplementing testosterone in women is complicated by many factors. An age-related decrease in adrenal androgen precursors generates markedly reduced intracellular testosterone

activity (38,39). However, intracellular testosterone levels correlate poorly with serum testosterone levels because testosterone acts within the cell and is metabolized there, and only the metabolites spill back into the blood stream (39). This finding may contribute to the reason for conflicting studies regarding the relationship between testosterone (measured as serum levels) and sexual function or dysfunction. Furthermore, available testosterone assays for serum levels are neither accurate nor sensitive at the low levels of testosterone found in women (the assays were designed for the male range) (23). This lack of clarity applies whether bioavailable, free, or total testosterone levels are measured.

Illnesses that accompany aging may also have an impact on sexual dysfunction. However, the association is weaker than that between male erectile dysfunction and hypertension, hyperlipidemia, diabetes, and coronary artery disease. Some sexual activities (e.g., intercourse) or responses (e.g., orgasmic intensity) may be inhibited by arthritic, cardiac, or respiratory disorders.

Personality Factors

Studies have shown that, compared with functional women, those who have concerns about low levels of desire and arousability are characterized as having vulnerable self-esteem, high levels of anxiety and guilt, negative body image, introversion, and somatization (25). Studies tend not to identify psychopathology in women who report low desire (11). The clinical impression of women with orgasmic disorder is that many are extremely uncomfortable in conditions in which they are not in control of circumstances or their bodily reactions. **For many women with vaginismus, there is a phobic quality to the fear of vaginal penetration. A subgroup of women with vulvar vestibulitis showed a marked fear of negative evaluation by others, conscientiousness, and self-criticism, as well as an increase in somatization (40,41).**

Relationships

Most women who report loss of desire and arousability indicate that their partnerships are stable and satisfactory. However, an environment free of conflict, abuse, and the threat of separation or divorce is insufficient to nurture a woman's sexual desire. Commonly, the woman reports that her partner is not emotionally intimate with her and not willing to reveal his (or her) feelings, fears, and hopes. Additionally, the woman's need for eroticism and variety of sexual stimulation may not be met. Women frequently classify their relationship as being "very good friends." Such a context is insufficiently sexual for nurturing or triggering a woman's sexual desire. Change of partner has been shown to be a major factor in increasing women's desire and responsiveness, and there is a lessening of innate desire with the duration of a relationship (20,21). The woman's feelings for her partner is one of the major determinants of lack of distress about sex (24); similarly, the woman's feelings for her partner, or a change of partner, were major determinants of a woman's desire (20,24,42).

Sexual Dysfunction in the Partner

Multiple aspects of a woman's circumstances can influence her sexual function, and one of the most important aspects is sexual dysfunction in a male partner (43). **Successful treatment of a male partner's erectile dysfunction can result in reversal of the woman's sexual problems, including difficulties with sexual arousal, lubrication, orgasm satisfaction, and pain (32).**

Infertility

Infertility evaluation and assisted reproductive techniques can have negative effects on a woman's body image and feelings of sexual self-worth. Infertility may cause her to feel hopeless and sexually undesirable. The loss of sexual spontaneity resulting from the goal-oriented approach to sex while trying to conceive with scheduled intercourse may lead to sexual dysfunction. The stress of testing and waiting for results may disrupt emotional intimacy, causing further damage to sexual function. Unfortunately, these changes do not always reverse with a successful pregnancy. Often there are unresolved feelings of guilt over personal responsibility for the infertility and feelings of resentment of the multiple procedures required for women compared with one semen analysis for men.

Table 11.1 Medications Affecting Sexual Response	
Drugs with negative sexual effects	
<ul style="list-style-type: none"> • Antihypertensives: β-blockers, thiazides • Antidepressants: serotonergic antidepressants • <i>Lithium</i> • Antipsychotics • Antihistamines • Narcotics • Benzodiazepines • Oral contraceptives and oral estrogen therapy • Gonadotropin-releasing hormone (GnRH) agonists • <i>Spiroolactone</i> • Cocaine • Alcohol • Anticonvulsants 	
Drugs that appear to be prosexual	
<ul style="list-style-type: none"> • <i>Danazol</i> • <i>Levodopa</i> • Amphetamines • <i>Bupropion</i> 	

Drugs

Prescription and nonprescription medications, including alcohol and illicit drugs, can alter the normal sexual response (Table 11.1). Adjustments in dosage or formulation of

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medication may be required. A number of pharmacological agents might improve or reverse the loss of arousal, desire, and orgasm commonly associated with serotonergic antidepressants (SSRIs). A recent *Cochrane Review* could make no recommendations for women but did note that *bupropion* may be effective based on the results of one of two randomized controlled trials (44).

Table 11.2 Sex and Chronic Illness

<ul style="list-style-type: none"> • Biological disruption of the sexual response, e.g., multiple sclerosis damaging pelvic autonomic nerves
<ul style="list-style-type: none"> • Negative psychological consequences of the illness affecting sexual response, e.g., feeling sexually unattractive as a result of disfigurement from surgery, medication, stomas
<ul style="list-style-type: none"> • Increased fatigue
<ul style="list-style-type: none"> • Chronic pain
<ul style="list-style-type: none"> • Incontinence or stomas reducing sexual self-confidence
<ul style="list-style-type: none"> • Accompanying depressive illness
<ul style="list-style-type: none"> • Treatment of chronic illness, e.g., chemotherapy-inducing ovarian failure
<ul style="list-style-type: none"> • Limited mobility, e.g., arthritis precluding intercourse, Parkinson's disease precluding masturbation
<ul style="list-style-type: none"> • Cardiac or respiratory compromise such that orgasm or movements of intercourse cause angina or intense dyspnea

Chronic Illness

Chronic illness can affect sexual function in a number of ways (Table 11.2).

Chronic Pelvic Inflammatory Disease/Endometriosis

Chronic dyspareunia, remitting temporarily or not at all with surgical or medical therapy, typically is associated with loss of sexual motivation/interest. Although definitive therapy is the overall goal, encouragement of nonpenetrative sex is very important for preservation of the woman's sexual enjoyment, sexual self-esteem, and relationship.

Polycystic Ovarian Syndrome

There is no evidence that the higher androgen levels associated with polycystic ovarian syndrome (PCOS) afford protection from low sexual desire or low sexual arousability. Rather, a sample of 30 women with PCOS presenting for treatment for hirsutism were found to have levels of sexual desire significantly lower than those in the control group (45).

Recurrent Herpes

Fear of spreading an STD may reduce sexual motivation and arousability. Clear guidance regarding safer sexual practices is needed, along with a discussion of the causes of the woman's lowered sexual motivation. A recognized difficulty with recurrent herpes is viral shedding despite lack of skin lesions and uncertainty whether long-term antiviral therapy prevents shedding.

Lichen Sclerosis

Tethering of the clitoral hood, which occurs with lichen sclerosis, may cause pain with clitoral stimulation. When this skin disorder involves the introitus, it may cause dyspareunia or prevent entry of penis, dildo, or fingers. Topical corticosteroid administration is the primary treatment, although topical testosterone cream may be beneficial when loss of sexual sensitivity occurs.

Breast Cancer

Sexual dysfunction following breast cancer treatment is likely to persist more than 1 year after diagnosis of breast cancer (46). Chemotherapy appears to be responsible for most of the resulting sexual difficulties, including loss of desire, subjective arousal, vaginal dryness, and dyspareunia (47). A model for predicting sexual interest, function, and satisfaction after breast cancer has evolved from two large independent groups of breast cancer survivors (47). The most important predictors of sexual health were absence of vaginal dryness, presence of emotional well-being, positive body image, better quality of relationship, and lack of partner sexual problems. A temporary "medical menopause" from adjuvant gonadotropin-releasing hormone agonist treatment is associated with reversible sexual dysfunction (48). Use of *tamoxifen* does not consistently alter sexual function (49).

Diabetes

A systematic review of women with diabetes disclosed a lack of clear correlation between the degree of complication of disease and sexual dysfunction.

Psychophysiologic studies have not supported any difference between increases in congestion in response to erotic stimulation or increases in subjective arousal between women with and without diabetes (50). Nevertheless, in the clinical setting, higher rates of overall sexual dysfunction have been found in women with diabetes compared with women who do not have diabetes, but statistical significance was only met for the symptom of decreased lubrication (51). Significant predictors were the quality of the marital relationship and presence or absence of depression. It is clear that psychological as opposed to somatic factors largely account for sexual problems in women who have diabetes.

Hysterectomy

Simple Hysterectomy

Despite speculation that there might be different sexual outcomes depending on whether hysterectomy was vaginal, subtotal, or total abdominal, this difference has not been supported by recent studies (52,53). In a large prospective observational study of 413 women undergoing three different types of hysterectomy (vaginal, supracervical, and total abdominal hysterectomy), sexual pleasure was noted to improve in most women, independent of the type of hysterectomy (53). The prevalence of one or more bothersome sexual problems 6 months after vaginal, supracervical, and total abdominal hysterectomy was 43%, 41%, and 39%, respectively. The results of another prospective trial of 158 women randomized to total abdominal hysterectomy and 161 to supracervical abdominal hysterectomy showed no difference in sexual outcomes (52). A retrospective study of 108 women undergoing classic intrafascial supracervical hysterectomy and 125 undergoing total hysterectomy did not find any sexual benefits of classic intrafascial supracervical

hysterectomy over total hysterectomy (54). **There was no difference between groups in time from surgery to first intercourse, change in libido, sexual frequency, or frequency or degree of orgasm.** Overall, two thirds of the women in the study experienced either no change or an improvement in sexual function, regardless of which procedure was performed. Both this study and a study comparing total laparoscopic hysterectomy with laparoscopically assisted vaginal hysterectomy found similar effects on sexual function (55).

Radical Hysterectomy

Techniques have been developed to avoid the portions of the inferior hypogastric plexus in the cardinal and broad ligaments (56). The results of studies of the sexual outcome on women who underwent radical hysterectomy using these nerve-sparing techniques are now awaited. In one study, 12 women with simple hysterectomy and 12 with radical hysterectomy (Piver-Rutledge Class III) were compared with 17 sexually healthy women. All women were premenopausal, and very few had any symptoms of sexual dysfunction. The maximal increase in vaginal congestion was highest in the control group and lowest in the women who underwent nonnerve-sparing radical hysterectomies. However, subjective arousal was lowest in women who underwent simple hysterectomy, and there was no difference in subjective arousal or excitement levels between women in the control group and those who had received radical hysterectomies (57). Early results of ongoing studies of women with cervical cancer who received either radical or simple hysterectomy show that the level of sexual dysfunction is associated with a tendency to monitor their gynecologic and other symptoms.

Sexual dysfunction is associated with their general level of distress and is not related to surgery type, use of radiation, or whether bilateral oophorectomy was performed (58).

Cancer of the Cervix

Sexual symptoms encountered in women with cancer of the cervix include reduced vaginal lubrication secondary to surgical menopause or radiation damage. A study conducted in Croatia has shown the importance of fear of dyspareunia. Of 210 women treated with combinations of surgery, radiation, and chemotherapy, 50% reported a marked fear of pain. However, only six patients identified actual dyspareunia and only three patients found penetration impossible (59).

There is marked synergy between cancer of the cervix and sexual abuse as a cause of sexual dysfunction (60). An absence of sexual satisfaction was reported by 20% of women with neither abuse nor cancer of the cervix, by 31% of women who had been sexually abused and did not have cancer of the cervix, by 28% of women with cancer of the cervix who had not been abused, but by 45% of women with a history of both abuse and cancer of the cervix. The lack of sexual satisfaction resulted in a decrease in well-being in

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18% of women with neither a history of abuse nor cancer of the cervix, 39% of women who had been abused and did not have cancer of the cervix, 23% of women with cancer of the cervix who had not been abused, and in 44% of women with a history of both abuse and cancer of the cervix. Dyspareunia was extremely rare in women without cancer of the cervix, but it was reported by 12% of those with cancer of the cervix and by 30% of those with cancer of the cervix and past sexual abuse.

Pregnancy

Physical, emotional, and economic stressors of pregnancy may negatively affect emotional and sexual intimacy. Sexual attitudes and behavior during pregnancy

and postpartum are influenced by sexual value systems, folklore, religious beliefs, physical changes, and medical restrictions. In the absence of preterm labor, antepartum bleeding, or an incompetent cervix, there is no evidence that sexual activity, orgasm, or intercourse increases the risk of pregnancy complications. Normal changes that occur with sexual activity during pregnancy include increased breast tenderness, increased sensitivity to uterine contractions with orgasm, general discomfort, less mobility, and fatigue. Sexual satisfaction in pregnancy is closely related to feeling happy about the pregnancy, continuing to feel attractive, and understanding that in healthy pregnancy sexual activity and orgasm do not harm the fetus.

Toward the end of the third trimester the need for closeness, emotional support, and nurturing may be far greater than any desire for orgasms or intercourse. Difficulties may arise from the partner's reaction to the woman's pregnancy, the physical changes of pregnancy, lack of information regarding sex and pregnancy, and lack of direction from the physician when complications arise. **A general lessening of sexual desire in both pregnancy and the postpartum period is common and considered normal.** A prospective analysis of sexual function of 40 healthy pregnant women showed a reduction in desire and in all aspects of sexual response beginning in the first trimester, changing little in the second, and reducing further in the third trimester (61).

Postpartum

The ongoing vaginal bleeding and discharge, perineal discomfort, hemorrhoids, sore breasts, and decreased vaginal lubrication associated with nursing, compounded by fatigue from disturbed nights, all contribute to decreased motivation for sexual activity. Further complicating factors include fear of waking the baby, a decreased sense of attractiveness, change of body image, or mood change. Many couples resume sexual activity and include intercourse by 6 to 8 weeks postpartum, but some couples wait as long as a year before resuming their prepregnancy level of sexual intimacy. Typically women who nurse report less sexual activity and less satisfaction than those who bottle feed. **There is no definite correlation between sexual activity and method of delivery,** although women who undergo cesarean birth tend to resume intercourse earlier (62). Few studies record whether episiotomy influences sexual function.

Physicians can provide considerable help to patients and their partners by acknowledging and discussing the normal fluctuations in sexual desire and frequency of sexual activity during and after pregnancy. **Couples should generally be encouraged to continue their usual patterns of lovemaking during pregnancy if they are emotionally and physically comfortable and there are no contraindications to either orgasm or intercourse.**

Assessment of Sexual Problems

Despite the importance of issues relating to sexuality, many women may find it difficult to talk to their physicians about sexual concerns, and many physicians are

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uncomfortable discussing sexual issues with their patients. In one survey, 71% of adults said they thought their doctor would dismiss any concerns about sexual problems they might introduce, and 68% said they were afraid that discussing sexuality would embarrass their physician (63). Through the use of a structured questionnaire and review of the records of 1,065 women who consecutively attended 37 family practices in areas of high, medium, and low socioeconomic status, 40% of women were found to have at least one form of sexual dysfunction according to diagnostic criteria of the international statistical classification of disease (ICD-10). Only 4% had a prior entry in their medical record relating to sexual

problems (29).

There are numerous reasons physicians are reluctant to discuss issues relating to sexuality with their patients. Physicians may be anxious about their perceived inability to treat sexual problems or feel that they have too little time to accurately assess sexual concerns in their practice. They also may be distressed by their patients' history of sexuality-related violence or may experience personal discomfort when discussing sexual matters with their patients. Not asking about sexual function suggests to patients that sexuality is not important and should not to be discussed, however, which results in a missed opportunity for counseling about sexuality as well as other important related issues.

Asking about sexual concerns gives physicians an opportunity to educate patients about the risk of STDs, encourage safer sex practices, evaluate the need for contraception, dispel sexual misconceptions, and identify sexual dysfunction. Many sexual concerns can be resolved by providing factual information and reassurance. Management of sexual dysfunction, however, requires appropriate biopsychosocial assessment and intervention. Even when patients currently have no sexual problems, they learn that future sexual issues can be addressed in a professional, confidential, and nonjudgmental setting.

Interviewing Techniques

To be comfortable enough to establish rapport and trust with patients, physicians should be familiar with the components of a sensitive, detailed, sexual assessment and the general principles of management of dysfunction. Good listening skills and attention to nonverbal cues are helpful. Physicians should use straightforward language that patients can understand and acknowledge that many people find it difficult to discuss these sensitive, intimate, and extremely common issues.

A few open-ended questions can initiate the subject of sexual function (Fig. 11.2). Sexual inquiry is part of the medical history taken during a routine gynecologic assessment. Listed in Table 11.3 are some examples of screening questions related to particular obstetric–gynecologic circumstances.

Optimally, the detailed assessment is obtained from both partners. Questions can be directed to the couple or the individual partners, depending on the circumstances (Table 11.4). When dyspareunia is present, detailed questioning is necessary (Table 11.5).

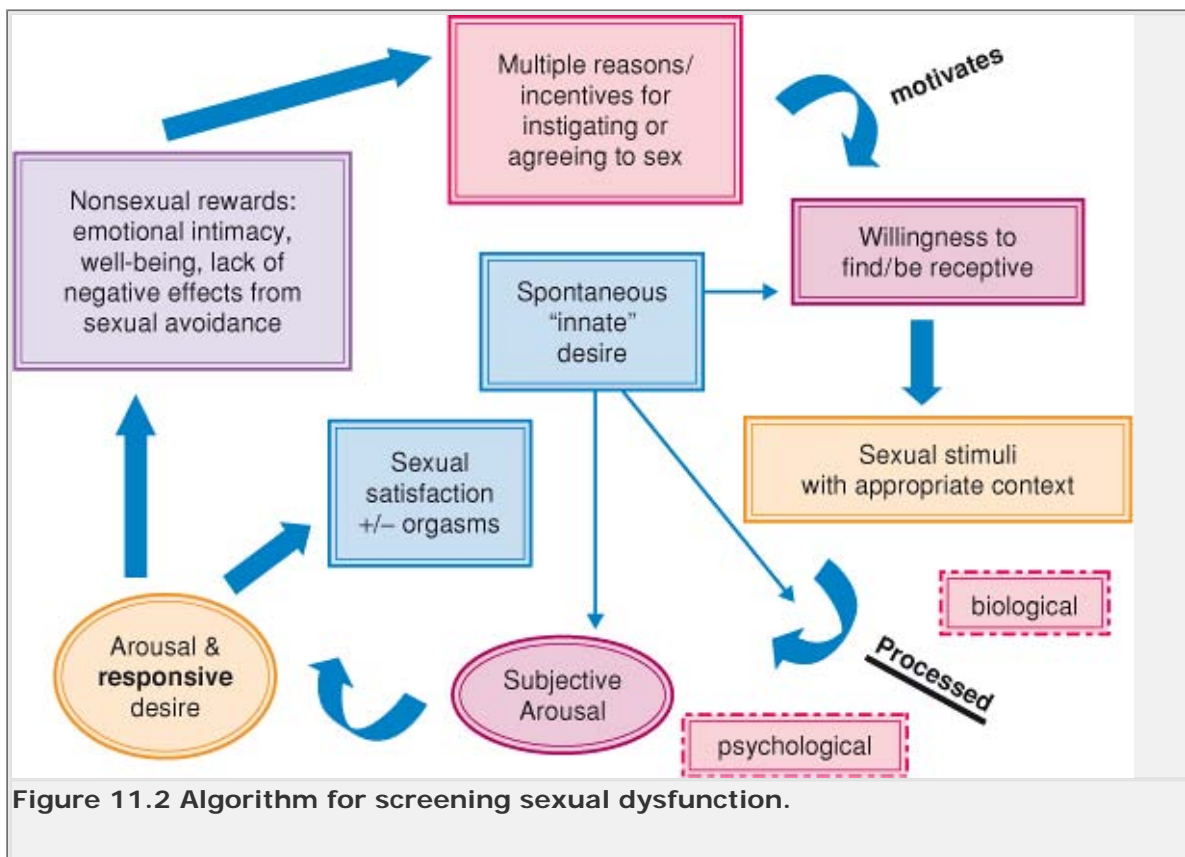
Physical Examination

Routine pelvic examination is an essential component of general medical care; however, this is not the case with women who seek care for sexual concerns. Given the prevalence of negative past sexual experiences, including abuse, **a pelvic examination should be performed only in the presence of a definite indication, and the procedure should be clearly explained to the patient** (Table 11.6). Management of dyspareunia mandates careful vulvar, vaginal, and pelvic examination. It should be noted that although a physical examination can confirm normal anatomy and the healthy nonaroused state of the

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genitalia, it does not confirm healthy sexual function. Nevertheless, such an examination can be both instructive and therapeutic.



Diagnostic Criteria

Similar to phases of sexual response overlap, types of women's sexual dysfunctions also overlap (11,29). The Second International Consensus on Sexual Dysfunctions in Men and Women (18) provides evidence-based recommendations for the diagnosis of sexual dysfunction and encompasses the recently proposed revisions to the American Psychiatric Association's Diagnostic and Statistical Manual Text Revised (DSM-IV-TR) definitions of women's sexual dysfunction (64,65) (Table 11.7).

Each disorder is then further classified by the following descriptors:

- **Lifelong or acquired**
- **Generalized or situational**
- **The degree of distress—mild, moderate, or marked**
- **Presence of contextual factors**
 - **Past factors from developmental history affecting psychosexual development**
 - **Present contextual factors—interpersonal, environmental, societal, and cultural**
 - **Medical factors**

Table 11.3 Screening for Sexual Problems

Situation in which Screening Question Is Necessary	Suggested Screening Question
Before surgery or instituting medication or hormone therapy	<i>Your surgery or medication is not expected to interfere with your sexual function. I need to check, though, whether you have any difficulties now with sexual desire, arousal, or enjoyment; or is there any pain?</i>
Routine antenatal visit	<i>Women's sexual needs can change during pregnancy. Do you have any problems or questions now? There is no evidence that intercourse or orgasm leads to miscarriage. Of course, any bleeding or spotting will require checking and postponing sexual activity until we have evaluated you. Many women find fatigue and/or nausea reduce their sexual life in the first 3 months, but usually things get back to normal for the middle 3 months and sometimes right up to term.</i>
Complicated antenatal visit	<i>These complications may well have already caused you to stop being sexual. Specifically, you should not (have intercourse/have orgasms).</i>
After one or more miscarriages	<i>Some women temporarily lose desire for sex after a miscarriage—this is quite normal. Many couples concentrate on affectionate touching while they both grieve about what has happened. Do allow yourselves some time. If any sexual problems persist, we can address them.</i>
Infertility	<i>All this testing and timed intercourse and disappointment, plus the financial burdens that are coming up, can be very stressful on your sex life. Try to have times when you and your partner are sexual just for pleasure and intimacy's sake—not when you are trying to conceive. Do you have any problems now?</i>
Postpartum	<i>It may be some weeks or months before you have the energy to be sexual, especially if your sleep is really interrupted. This is normal. If problems persist, or if you have pain, this can be addressed. Do you have any questions right now?</i>
Perimenopause or postmenopause	<i>We know many women have very rewarding sex after menopause—more time, more privacy. If you find the opposite or you begin to have pain or difficulty getting aroused, these things can be addressed. Do you have any concerns now?</i>

Woman who is depressed	<i>I know you are depressed right now, but our studies tell us that sex is still important for many women who are depressed. We also know that some of the medications we prescribe interfere with sexual enjoyment. Do you have any problems right now?</i>
Chronic illness	<i>Arthritis/multiple sclerosis can interfere with a woman's sex life. Are you having any problems?</i>
Potential damaging surgery	<i>Obviously the focus right now is to remove your cancer entirely when we do your surgery. The nerves and blood vessels that allow sexual sensations and lubrication may be temporarily and sometimes permanently damaged. If when you have recovered you notice any sexual problems that persist, they can be addressed. Do you have any concerns now?</i>
Bilateral oophorectomy	<i>Your surgery will remove a major source of estrogen and approximately one half of the testosterone your body has been making. Testosterone will still be made by adrenal glands (small glands on top of the kidneys), and some of this gets converted into estrogen. Many women find that these reduced amounts of sex hormones are quite sufficient for sexual enjoyment, but others do not. Any sexual problems that do occur almost certainly can be addressed. Do you have any problems now?</i>

Table 11.4 Biopsychosocial Assessment of Sexual Dysfunction

<i>Sexual problem in patient's own words</i>	Clarify further with direct questions; give options rather than leading questions.
<i>Duration, consistency, priority</i>	Are problems present in all situations, and which is most severe?
<i>Context of sexual problems</i>	Emotional intimacy with partner, activity/behavior just before sexual activity, privacy, safety, birth control, risk of STD, usefulness of sexual stimulation, sexual skills of partner, sexual communication, time of day
<i>Rest of each partner's sexual response</i>	Check this currently and before the onset of the sexual problems—sexual motivation, subjective arousal, enjoyment, orgasm, pain, and erection and ejaculation in male partner
<i>Reaction of each partner to sexual problems</i>	How each has reacted emotionally, sexually, and behaviorally
<i>Previous help</i>	Compliance with recommendations and effectiveness
<i>Reason for presenting now</i>	What has precipitated this request for help
<i>Assessment of Each Partner Alone</i>	

Partner's own assessment of the situation	Sometimes it is easier to acknowledge symptoms, e. g., total lack of desire, in the partner's absence
Sex response with self-stimulation	Also ask about sexual thoughts and fantasies
Past sexual experiences^a	Positive, negative aspects
Developmental history^a	Relationships to others in the home while growing up, losses, traumas, how they coped. To whom (if anyone) was this person close? Who showed them affection, loved them, respected them? Clarify if some of these themes are playing out now in the current sexual relationship.
Ask about sexual, emotional, and physical abuse^a	Explain abuse questions are routine and do not necessarily imply causation of the problems.
^a These items of the single patient interview may sometimes be omitted (e.g., for a recent problem after decades of healthy sexual function).	

Many of the sexual problems couples encounter are due to a deficit of knowledge or experience, sexual misconceptions, or inability of the couple to communicate about their sexual preferences. Brief counseling and education by the obstetrician-gynecologist regarding the circular sex response cycle can identify the areas where sexual dysfunction can occur.

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The PLISSIT Model

Although gynecologists may sometimes need to provide detailed management for certain conditions (e.g., for the chronic dyspareunia of vulvar vestibulitis syndrome [VVS]), frequently the first two levels of a model known as PLISSIT are sufficient to address women's sexual problems. The model is as follows:

- **Permission.** The consent of permission is the validation of the patient's concerns and confirmation that the gynecologist's office is an appropriate setting to address them.
- **Limited Information.** The patient is provided with information about sexual physiology and behavior so misunderstandings, myths, lack of knowledge, and inadequate sexual skills can be addressed.
- **Specific Suggestions.** This stage may involve prescribing hormones and medications, advising different forms of sexual stimulation, evaluating sexual context, reeducating patients about specific attitudes and practices, addressing mental health issues, and identifying interpersonal factors.
- **Referral for Intensive Therapy.** This step may be necessary for intrapsychological issues stemming from childhood that impair women's ability to be aroused and interest/desire, including past traumas and abuse, couples who need more specialized help in sexual communication, and male sexual dysfunctions.

Table 11.5 Assessment of Dyspareunia: By History

- Ask if vaginal entry is possible at all (i.e., with finger, penis, speculum, tampon)
-
- Ask if sexual arousal is experienced when intercourse is attempted and as it progresses.
-
- Ask exactly when the pain is experienced:
 - —With partial entry of the penis—With attempted full entry of penile head
 - —With deep thrusting
 - —With penile movement
 - —With the man's ejaculation—With the woman's subsequent urination
 - —For hours or minutes after intercourse attempts
-
- Ask if on some occasions there is less/no pain, and if so, what is different?

As an example of a PLISSIT approach, a woman with chronic dyspareunia from VVS is first given validation of her pain and is provided with the information that VVS is common

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and that many women find intercourse is precluded by the pain. The patient and her partner are encouraged to focus on nonpenetrative aspects of lovemaking. The next level is the provision of limited information about chronic pain mechanisms, the role of psychological stress, and genetic and possible immune factors. Specific suggestions could include encouragement to remove intercourse as one of the ways the couple interact sexually, prescription of medications for chronic pain, prophylaxis for overgrowth of candidiasis when this is relevant, and referral to a pelvic muscle physiotherapist if necessary. Referral for intensive therapy may be indicated for the woman in whom depression is precipitated, for couple counseling if the relationship cannot cope with the stress, or to a gynecologist specializing in vulvar surgery if vestibulectomy is considered.

Table 11.6 Physical Examination for Sexual Dysfunction

General exam	Signs of systemic disease leading to low energy, low desire, low arousability, e.g., anemia. Bradycardia and slow relaxing reflexes of hypothyroidism. Signs of connective tissue disease, such as scleroderma or Sjören's, which are associated with vaginal dryness. Disabilities that might preclude movements involved in caressing a partner, self-stimulation, intercourse. Disfigurements/presence of stomas; catheters that may decrease sexual self-confidence, leading to low desire; low arousability.
External genitalia	Sparsity of pubic hair, suggesting low adrenal androgens. Vulval skin disorders, including lichen sclerosis, which may cause soreness with sexual stimulation (e.g., when it involves the clitoral hood). Cracks/fissures in the interlabial folds suggestive of chronic candidiasis. Labial abnormalities that may cause embarrassment/sexual hesitancy (e.g., particularly long labia or asymmetry).

Introitus	Vulval disease involving introitus (e.g., lichen sclerosis). Recurrent splitting of the posterior fourchette manifest as just visible white lines perpendicular to fourchette edge. Abnormalities of the hymen (e.g., hymenal band across the introitus). Adhesions of the labia minora. Swellings in the area of the major vestibular glands. Allodynia (pain sensation from touch stimulus) of the crease between the outer hymenal edge and the inner edge of the labia minora (typical of vulvar vestibulitis). Allodynia of the Skene's duct openings. Presence of cystocele, rectocele, or prolapse interfering with the woman's sexual self-image. Inability to tighten and relax perivaginal muscles (often associated with hypertonicity of pelvic muscles and midvaginal dyspareunia). Abnormal vaginal discharge associated with burning dyspareunia.
Internal exam	Pelvic muscle tone. Presence of tenderness trigger points on palpating deep levator ani as a result of underlying hypertonicity.
Full bimanual exam	Presence of nodules and/or tenderness in the cul-de-sac or vaginal fornix, or along uterosacral ligaments. Retroverted fixed uterus as causes of deep dyspareunia. Tenderness palpating posterior bladder wall from anterior vaginal wall suggestive of bladder pathology.

Table 11.7 Revised DSM-IV Definitions of Women's Sexual Dysfunction

Diagnosis	Definition	Comments
Sexual desire/interest disorder	Absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies <i>and</i> a lack of responsive desire. Motivations (here defined as reasons/incentives) for attempting to become sexually aroused are scarce or absent. The lack of interest is beyond a normative lessening with life cycle and relationship duration.	Minimal spontaneous sexual thinking or desiring of sex ahead of sexual experiences does not necessarily constitute disorder. Additional lack of responsive desire is integral to the diagnosis.
Combined sexual arousal disorder	Absent or markedly reduced feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation and absent or impaired genital sexual arousal (vulval swelling and lubrication).	There is minimal sexual excitement (subjective arousal) from any type of stimulation—erotic material, stimulating the partner, genital and nongenital stimulation. There is no awareness of the reflexive genital vasocongestion.
Subjective sexual arousal disorder	Absent or markedly reduced feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation. Vaginal lubrication and other signs of physical response still occur.	Despite lack of sexual excitement/subjective arousal, lubrication is noted by the woman or partner. Intercourse is comfortable without use of external lubricant.

Genital arousal disorder	Absent or impaired genital sexual arousal—minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. <i>Subjective sexual excitement</i> still occurs from nongenital sexual stimuli.	Subjective arousal (sexual excitement) from nongenital stimuli (erotica, stimulating the partner, receiving breast stimulation, kissing) is key to this diagnosis. Early studies indicate reduced vasocongestion in some but not all cases. Loss of sexual sensitivity of physiologically congested tissues accounts for others.
Orgasmic disorder	Despite the self-report of high sexual arousal/excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations, or marked delay of orgasm from any kind of stimulation.	Women with arousal disorders frequently do not experience orgasm. Their correct diagnosis is one of an arousal disorder.
Vaginismus	Persistent or recurrent difficulties of the women to allow vaginal entry of a penis, finger or any object despite the woman's expressed wish to do so. There is often (phobic) avoidance and anticipation/fear/experience of pain, along with variable and involuntary pelvic muscle contraction. Structural or other physical abnormalities must be ruled out/addressed.	Confirmation of this diagnosis is not possible until there has been therapy sufficient to allow a careful introital and vaginal examination. It is a presumptive diagnosis initially.
Dyspareunia	Persistent or recurrent pain with attempted or complete vaginal entry and or penile vaginal intercourse	There are many causes, including localized provoked vestibulodynia (vulvar vestibulitis syndrome) and vulvar atrophy from estrogen deficiency.
<p>From: Dunn KM, Croft PR, Hackett GI. Sexual problems: a study of the prevalence and need for health care in the general population. <i>Fam Pract</i> 1998; 15: 519–524.</p> <p>From: Basson R, Leiblum S, Brotto L, et al. Definitions of women's sexual dysfunctions reconsidered: advocating expansion and revision. <i>J Psychosom Obstet Gynaecol</i> 2003; 24: 221–229</p>		

Sexual Dysfunction

Sexual problems are common in the general population in the United States. Surveys have found that approximately 30% of women report they lack interest in sex (11,63,66,67,68,69). Almost as many find sex affords little pleasure (3). Approximately 10% to 15% of women experience chronic dyspareunia (3,64). Few surveys ask questions about sexual excitement/subjective arousal, focusing instead on just

one component of arousal, vaginal lubrication. One study of a nationally representative sample of 979 women aged 18 to 70 years found 17% identified problems with arousal (as distinct from vaginal dryness) (64). Insufficient lubrication is reported by 10% to 30% of women, which approaches the incidence postmenopause, and lack of orgasm is reported by 20% to 27% of women (2,3).

There are two important caveats regarding prevalence of sexual dysfunctions: first, comorbidity is typical (11,29), and second, not all women reporting a lack of interest/desire/arousal/orgasm see it as a problem or are distressed by it. Older women are less distressed than younger women about lack of sexual desire and interest (29). Studies show a correlation between sexual problems and poor self-esteem, poor physical and emotional health, being unmarried and less educated, having experienced sexual victimization, being sexually inexperienced, having negative experiences in prior sexual relationships, and not enjoying physical affectionate contact (3,66).

The duration of ongoing sexual difficulties (e.g., lasting more than 6 months) also is relevant. A study of women younger than 44 years of age in Great Britain found that although 41% of women reported lack of sexual interest for at least 1 month in the past year, only 10% reported it lasting longer than 6 months (66). Women who reported inability to experience orgasm for durations of 1 month and 6 months were 14.4% and 3.7%, respectively.

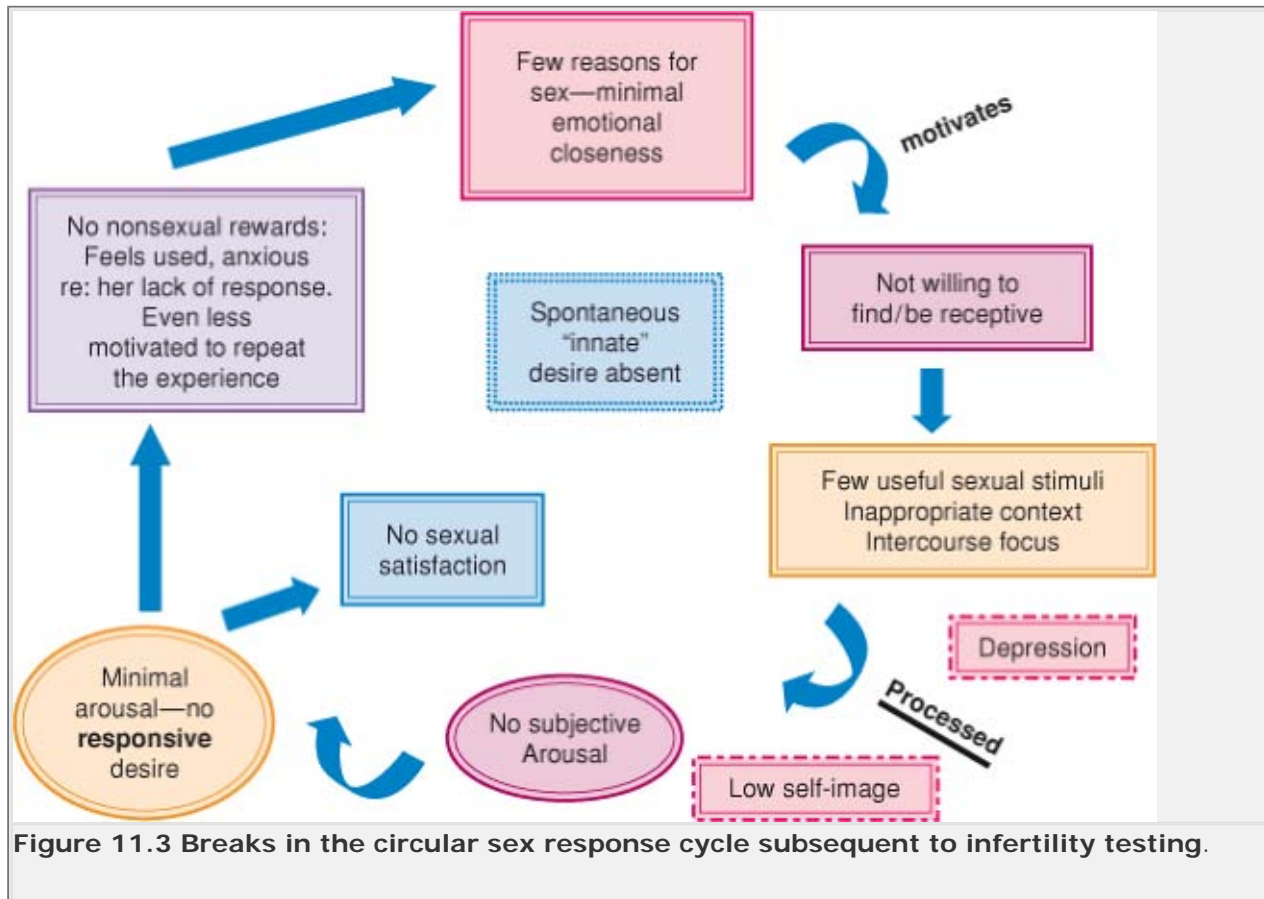
Chronic dyspareunia ranges in prevalence from 8% to 22% and decreases with age. Unexplained vulvar burning that interferes with intercourse, probably resulting from vulvar vestibulitis in most women, is thought to affect approximately 9% of women, with approximately 5% of women experiencing this condition before age 25 (68). Not surprisingly, most women with chronic dyspareunia perceive it as a problem.

Sexual Desire and Arousal Disorders

Construction of the woman's sex response cycle showing the various breaks can be highly therapeutic for the woman and her partner. Figure 11.3 shows the various breaks subsequent to infertility testing. The couple learns that it is "normal" for the woman to have low motivation to be sexual when emotional intimacy has suffered. If the issues distancing the couple cannot be addressed in the gynecologist's office (i.e., they extend over and beyond the common reactions to infertility testing and procedures), referral to a relationship counselor may be necessary. The gynecologist can address the sexual context and the type of stimulation that is provided. The need of most women for more nonphysical stimulation, more nongenital physical stimulation, and more nonintercourse sexual stimulation can be stressed. Privacy issues, time of day, and emotional closeness at the time of lovemaking can all be discussed. Factors personal to the woman that may be impairing her ability to be aroused, such as low sexual self-image and distractions, can be identified. Referral may be necessary when low self-image appears ingrained and stems from developmental factors. Biological factors influencing arousability, including fatigue, medication effect, and depression, may be involved. Fears regarding outcome, such as lack of adequate birth control or partner dysfunction, can be identified. Inquiring about the patient's thoughts at the time of potential lovemaking can be helpful. Some women admit to evoking negative thoughts or allowing spontaneously emerging negative thoughts to intrude when there is a sexual opportunity (70). Guilt about sex and about women having sexual pleasure may be present. If the woman is a new mother, she may feel on one level

that sex now is "wrong." Experiences of assisted reproduction technique or delivery may lead to the woman feeling loss of control; this in turn may lead to a need to regain control in all aspects of her life, which may suppress her sexual feelings. Insight-oriented psychotherapy may

allow patients to identify the negative feelings that inhibit erotic impulses (11). Meeting with a couple for a few sessions to assess their sexual knowledge, attitudes, and practices is often beneficial.



Genital Arousal Disorder

Management of the “genital deadness” of genital arousal disorder is unclear. Early research suggests that some of these women have demonstrably reduced genital vasocongestion in response to erotic stimuli (71). Those with reduced vasocongestion may benefit from investigational use of a phosphodiesterase inhibitor (71). Unfortunately, the role in clinical practice of psychophysiological study to monitor increases in pelvic vasocongestion in response to erotic stimuli is unclear, and these tests usually are not available. When local (or systemic) use of estrogen does not relieve the lack of genital sensitivity, the investigational use of phosphodiesterase inhibitor, with precautions against concomitant use of nitrates or alpha blocking agents, may be appropriate. Similarly, the investigational use of local testosterone (e.g., 2% testosterone applied to the clitoral area) has not been validated with scientific study. One theory is that the loss of genital sensitivity, despite physiological congestion, may be related to lack of androgen effect in the vulva.

Orgasmic Dysfunction

Lifelong orgasmic disorder is more common than acquired loss of orgasm. Some women acquire orgasmic dysfunction in association with relationship problems, depression, substance abuse, medication (especially use of SSRIs), or chronic illness (e.g., multiple sclerosis). Aside from those using SSRIs, most women who experience lack of orgasm are found on careful questioning to have modest degrees of subjective excitement (i.e., their true diagnosis is either subjective or combined arousal disorder). Sometimes women

just need reassurance that most couples do not experience orgasm simultaneously, that most women experience orgasm far more easily from direct clitoral stimulation, and that this does not constitute dysfunction.

Common causes of lack of orgasm include obsessive self-observation and monitoring during the arousal phase, sometimes accompanied by anxiety and distracting negative and self-defeating thoughts (72). The woman may be so intent on monitoring her own and her partner's response and concerned about "failing" that she is unable to allow her natural reflexes to take over and trigger an orgasm. Lack of orgasm may be related to negative feelings toward sexuality, low self-esteem, poor body image, a history of sexual abuse, and fear of losing control, as well as ineffective sexual technique. **The only evidenced-based therapy is encouragement of self-stimulation, accompanied by erotic fantasy: so-called directed masturbation.** Several excellent self-help books are available to help women become orgasmic through self-stimulation (73). A vibrator may be helpful if the plateau of high arousal is reached but there is still no orgasmic release. When the woman has experienced orgasm with self-stimulation with or without the use of a vibrator, she may or may not be able to teach the technique to her partner. Issues of trust may then surface, and more intense psychological help may be needed.

Sexual Pain Disorders

Vaginismus

Vaginismus is an involuntary reflex precipitated by real or imagined attempts at vaginal entry. It may be generalized, in which the woman is unable to place anything in her vagina, even her own finger or a tampon, or it may be situational, in which she can use a tampon and can tolerate a pelvic examination but cannot have intercourse. Couples frequently cope with this difficulty for many years before they seek help and then do so to begin a family. Often there are no obvious circumstances predisposing to vaginismus, such as an unpleasant past sexual experience or trauma, sexual abuse, or a painful first pelvic examination. Despite the theories, there is no scientific evidence that vaginismus is secondary to religious orthodoxy, negative sexual upbringing, or concerns about sexual orientation. Women with vaginismus typically have an extreme fear of vaginal entry and misconceptions about their anatomy and the size of their vagina. They fear that harm will come from something the size of a penis entering the vagina and similarly fear they would be damaged by vaginal delivery.

The diagnosis of vaginismus is provisional until a very careful introital and vaginal examination can be done. This is not possible until the woman has learned to be able to abduct her thighs, open the labia with her fingers or permit the examiner to do so, and to tolerate introital touch. The therapy for vaginismus must begin before the diagnosis is confirmed:

- **Encourage the couple to engage in sexual activities that exclude any attempt at intercourse.** They may need to again have "dates" and deliberately provide sexual contexts.
- **Explain to the patient the reflex contraction of pelvic muscles around the vagina to touch, especially when touch has been associated only with negative emotions and physical pain.** These women rarely use tampons and avoid the introitus and vagina in sexual play and thus have not experienced any neutral or positive sensations from this area of their bodies.

- **Institute self-touch on a daily basis for a few minutes as close to the vaginal opening as possible.** This may be done while the woman is in the bathtub or relaxing by herself on the bed. This is not sexual, and at first it will be highly anxiety provoking. Providing she does this daily, the anxiety will quickly decrease.

- **Suggest adding visual imagery to the previous exercise** so that she imagines being able to have a limited vaginal examination, sitting up on the couch at about a 70-degree angle to, with the aid of a mirror, view the vaginal opening and separate her labia, and be in control of what happens.

- **As soon as she is ready, perform the partial vulvovaginal examination as in step 4.** If possible, encourage her to touch the vagina, moving her finger past the hymen, possibly afterward doing the same with the physician's gloved finger.

- **Once the vagina has been adequately examined, prescribe a series of vaginal inserts of gradually increasing diameter.** When symptoms suggestive of VVS are also present—especially burning with semen ejaculation, dysuria, or vulvodynia after intercourse attempts—she should use only the smallest insert before a repeat examination takes place.

- **Repeat the examination with the woman checking for allodynia with a cotton swab.** Sometimes the physician can do this; it depends entirely on the amount of anxiety and apprehension the woman retains. However, the number of false-positive findings for allodynia can be limited if the patient touches the rim of the vaginal opening. Vestibulitis or other gynecologic findings should be treated. Once the patient is able to use larger inserts, the following steps can be undertaken:

- **Encourage the woman to allow her partner to assist her in placing the insert in her vagina.**
- **Encourage the couple during their sexual times to briefly use the insert** (to prove to her that the insert will still go in when her body is physiologically aroused).
- **Once she has used the insert on a number of occasions during sexual play, encourage her to follow it immediately with insertion of her partner's penis.** It is usually preferable for the woman to hold her partner's penis in the same position she used with the insert and to insert the penis herself. He must allow his pelvis to move forward with gentle pressure as she tries to insert it. The use of external lubrication is advised in these first attempts at penile entry.

Phosphodiesterase type 5 inhibitors may be used to treat temporary situational partner erectile dysfunction that occurs at the crucial moment when the woman is finally able to accommodate her partner's penis.

Dyspareunia

Dyspareunia, one of the most common types of sexual dysfunction seen by gynecologists, may affect two thirds of women during their lifetime (74).

Because dyspareunia is a psychophysiological condition, both psychological and physical factors must be considered in patient assessment. Generally, women with dyspareunia report more physical symptoms, psychological distress, and relationship issues than women who do not have pain during intercourse (75). Some women with VVS have an intense need to excel in all areas of their life and are particularly self-critical (40). Such internal stressors are thought to be involved in the maintenance of this chronic pain condition.

There are three aspects to the management of dyspareunia.

- **Assisting the couple to have rewarding sexual intimacy even if initially intercourse is precluded.**
- **Identifying the psychological issues contributing to and arising from the chronic pain.**

- **Treating, whenever possible, the underlying pathophysiology that has triggered the chronic pain circuits.**

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It is helpful to clarify that the popular depiction of sex as foreplay followed by "real sex" (i. e., intercourse) is not the reality for many sexually satisfied couples. The couple can be encouraged to consider the many varieties of human sexual interaction and ways of giving and receiving genital and nongenital sexual pleasure. It is important for the couple to see removal of intercourse from the menu of sexual activity as an opportunity to be more explorative and creative, and not as a loss.

Psychological Factors

Psychological factors contributing to dyspareunia include:

- **Developmental factors** (e.g., upbringing that invested sex with guilt and shame)
- **Traumatic factors** (e.g., past physical, sexual, or emotional abuse)
- **Relationship factors** (e.g., anger or resentment toward the sexual partner)

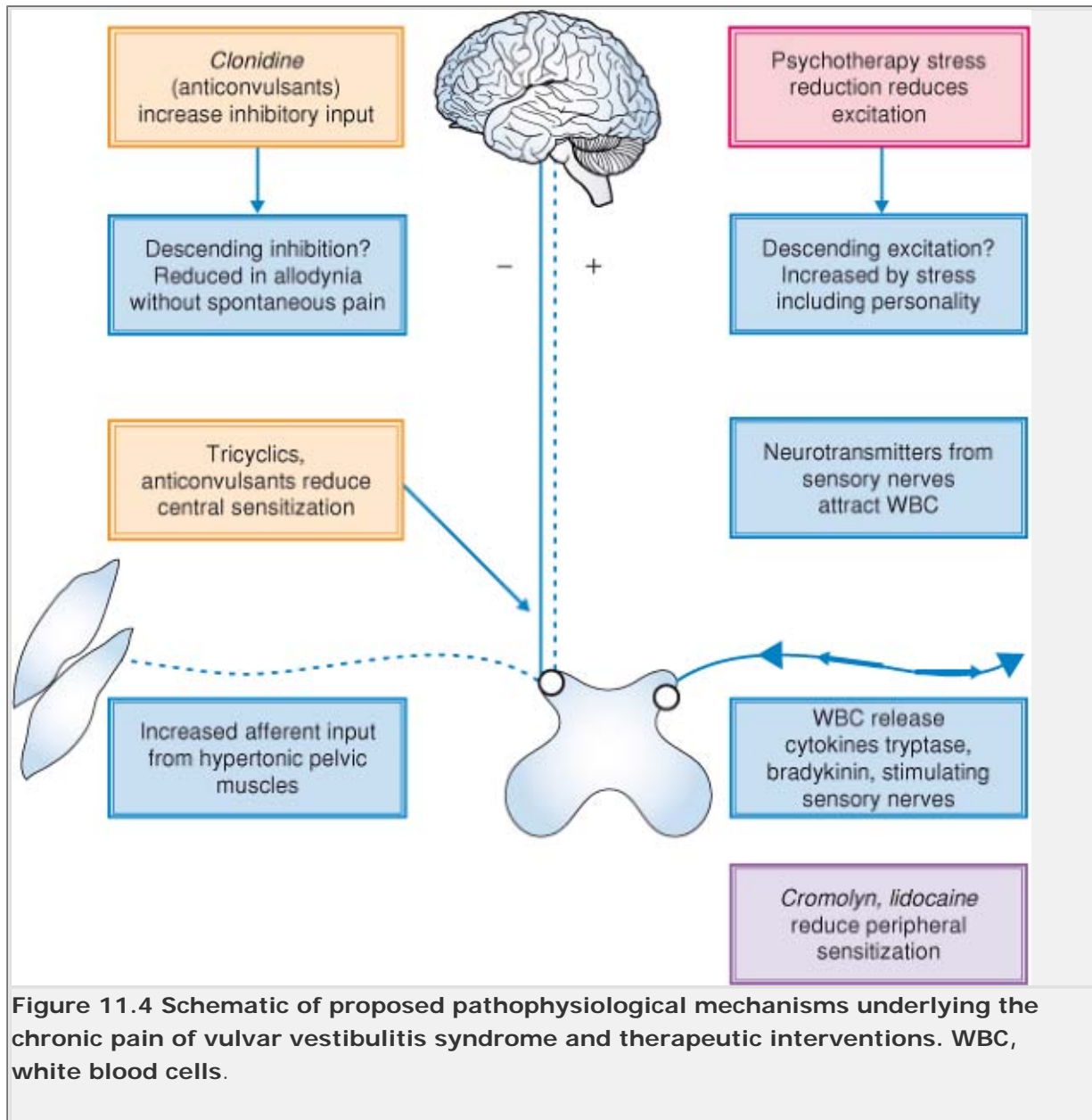
The goal of the assessment is to clarify the extent to which these three factors contribute to dyspareunia. Once that has been established, relevant referral may be necessary.

Reactions to chronic pain include loss of sexual self-confidence, guilt, anger, resentment, and feeling "used" when sexual activity with penetration continues, despite the presence of pain. It is important that the physician allows these negative emotions to be expressed (this is what referred to as "permission" in the PLISSIT model) and their cause validated so that the woman can move on to accepting her situation and finding ways of triggering and expressing her sexuality. It is important to include the partner in the assessment and evaluation of chronic dyspareunia, allowing his feelings to be addressed and his compliance with nonpenetrative sex encouraged. The couple rendered emotionally distant because of chronic dyspareunia may find it difficult to adapt to alternative forms

of lovemaking.

Underlying Pathophysiology

The pathophysiology of the most common type of dyspareunia, VVS, is unclear. The current understanding is that there is neurogenic inflammation that has led to chronic pain circuits with both central and peripheral sensitization. This means that there are physical changes within the central nervous system that perpetuate the pain cycles and that can be targeted by chronic pain drugs. Figure 11.4 shows the different aspects of pathophysiology underlying VVS and the placement of medication and pelvic muscle physiotherapy.



Introital pain may be caused by conditions other than VVS. The differential diagnosis includes recurrent tears of the posterior fourchette, which may be treated with the topical application of estrogen or testosterone and, if necessary, a perineorrhaphy. Other diagnoses are congenital abnormalities, including a hymenal ring that is rigid, scar tissue (e.g., from episiotomy repairs), a vaginal septum, and, much more commonly, vaginitis or vulvitis, sometimes resulting from the use of over-the-counter vaginal sprays and douches.

One important common cause of dyspareunia is friction from inadequate genital sexual arousal. Estrogen deficiency with inadequate lubrication, progressing to loss of elasticity and thinning of the epithelium from vaginal atrophy, is another common cause. This condition is easily treated with local estrogen therapy. Deep dyspareunia resulting from pelvic disease, including endometriosis, is managed by treatment of the underlying conditions.

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Sexual Dysfunction Midlife and Later

Because sexual dysfunction in older women can be related to a variety of factors, broad-spectrum treatment approaches are needed in which individual, interpersonal, and sexual aspects can be addressed simultaneously. The following steps in therapy are recommended:

- **To encourage the woman to take responsibility for discovering what provides sexual arousal and to learn to guide her partner toward stimuli that are pleasurable to her now, as they may be different and less effective than the ones she enjoyed when she was a younger woman.**
- **To assist her to understand that a more rewarding outcome will increase her sexual motivation.** Factors relating to the couple's sexual style and even sexual dysfunction in the partner may need to be addressed.
- **To counsel her that women can begin rewarding sexual experiences in the absence of desire, which can be reassuring and therapeutic.**
- **To acknowledge that resentment, frustration, and disappointment toward her partner is therapeutic and may benefit from referral for relationship counseling.**

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- **To advise that deep-seated psychological distress from factors in her development or current refractory mood disorders may require referral to a psychologist/psychiatrist.**

Practical suggestions for aging patients might include taking a warm bath before lovemaking to loosen stiff joints, making love in the morning when the couple is less fatigued, or having neither intercourse nor orgasm as a necessary goal. Local estrogen supplementation can alleviate vaginal dryness, urinary tract symptoms, and dyspareunia, restoring vaginal cell health, decreasing PH, and increasing vulvar/vaginal blood flow. The aging couple should be encouraged to use low-key, more prolonged sexual stimulation because the rate of sexual response is slower. Systemic estrogen supplementation may improve insomnia and hot flashes, thus improving sexual function. **Because oral estrogen can decrease free testosterone levels by nearly 50% by increasing levels of sex hormone-binding globulin, topical estrogen is a preferable formulation for women with sexual difficulties.**

In women with sexual dysfunction associated with salpingo-oophorectomy, the first published study of testosterone supplementation to levels at or only slightly higher than those found

in premenopausal women showed improved arousability/response but not an increase in desire as in sexual thinking/fantasizing (8). Recent multicentered randomized controlled trials of naturally and surgically menopausal women have shown improved "total satisfying sexual activity" and improvement in the desire domain on the sexual questionnaires used (48,76,77,78,79).

Unwanted effects of testosterone include acne, hirsutism, deepening of the voice, clitoromegaly, alopecia, hepatotoxicity, and undesirable changes in lipoprotein levels. Women receiving supplemental testosterone should undergo long-term monitoring for these conditions. Given the data on increased insulin resistance with higher levels of endogenous androgens (80), insulin resistance must be carefully monitored, especially in obese women. Women should be prescribed the lowest effective dose of testosterone and counseled that the treatment is investigational (23). Currently, the transdermal route appears optimal. The need for simultaneous use of systemic estrogen is another confounding variable in view of the lack of safety/efficacy data in randomized controlled trials recruiting women who begin estrogen therapy using transdermal formulations for sexual symptoms at menopause.

Sexual Assault

Sexual assault of children and adult women has reached epidemic proportions in the United States and is the fastest growing, most frequently committed, and most underreported crime (81,82,83). Sexual assault is a crime of violence and aggression, not passion, and encompasses a continuum of sexual activity that ranges from sexual coercion to contact abuse (unwanted kissing, touching, or fondling) to forcible rape. **The terms *sexual abuse survivor* and *assault survivor* are preferable to *victim*.**

In a survey of female family practice patients, 47% reported some type of contact sexual victimization during their lifetime; 25% reported attempted rape, and 13% had been forcibly raped, many as children (84). Among battered women, approximately 68% experience marital rape as an element of their repetitive abuse (85). Uninvited sexual attention in the workplace is reported by 50% of women in the United States (86). Spousal rape is reported infrequently because of fear of retribution and economic dependency (87). Obstetrician-gynecologists should routinely inquire about a history of childhood sexual abuse or adult sexual assault. These experiences are common and often have a lasting and profound effect on a woman's mental and sexual function as well as her general health and well-being.

Childhood Sexual Abuse

Childhood sexual abuse has a profound and potentially lifelong effect on the survivor. Although most cases of childhood sexual abuse are not reported by the survivor or her family, it is estimated that as many as one third of adult women were sexually abused as children. Childhood sexual abuse is often accompanied by another type of household dysfunction, such as physical abuse, violence against other family members, or substance abuse by parental figures (83). **Younger children are more often exposed to genital fondling or noncontact abuse** (exhibitionism, forced observation of masturbation, or posing in child pornography), and **children older than 10 years of age are more likely to be forced to have intercourse or oral sex** (88). **As children age, they are more likely to experience sexual abuse outside the home and more likely to be victimized by strangers. As adolescents, women survivors of childhood sexual abuse are at risk for early unplanned pregnancy, STDs, prostitution, antisocial behavior, running away from home, lying, stealing, eating disorders, and multiple somatic symptoms.** These women are more likely to engage in health risk behaviors such as smoking, substance abuse,

and early sexual activity with multiple partners (89). They may be less likely to use contraception (90). Survivors often avoid pelvic examinations and are less likely to have Pap tests because of the association between vaginal examinations and pain. They often receive inadequate prenatal care and are more likely than women who have not been abused to experience suicidal ideation and depression during their pregnancies and to deliver smaller and less mature babies (83).

Obstetrician–gynecologists can assist their sexual assault patients by validating their feelings and concerns and giving them control over their examination. It is important to ask the patient for permission to perform the examination, give her the opportunity to have an advocate in the room with her, and let her know that she has the right to stop the examination at any time (83).

Survivors may be unable to trust or establish rapport with adults. Some women blame themselves for the abuse and come to believe that they are not entitled to assistance from others. Thus, they risk continuing to enter abusive relationships. **Women survivors of childhood sexual abuse often develop feelings of powerlessness and helplessness and may become chronically depressed.** They experience a high incidence of self-destructive behavior, including suicide and deliberate self-harm, such as cutting or burning themselves (83,91,92). The most extreme mental health symptoms in assault survivors are associated with the onset of abuse at an early age, frequent abuse over a long period, use of force, or abuse by a parent. Survivors are also at risk for becoming victimized again later in life (93). Of women who report being abused as children, 50% are abused again as adults. Women who are sexually abused as children carry the effects of abuse into adulthood. As adults, they have the same level of physical symptoms and psychological distress as women who do not report childhood sexual abuse but are currently experiencing sexual or physical abuse (94).

Women who have been sexually abused as children or sexually assaulted as adults often experience sexual dysfunction and difficulty with intimate relationships and parenting (95). Chronic sexual concerns may include fear of intimate relationships, lack of sexual enjoyment, difficulty with desire and arousal, and anorgasmia. Compared with women who have not been sexually assaulted, they are more likely to experience depression, suicide attempts, chronic anxiety, anger, substance abuse problems, dissociative personality disorder, borderline personality disorder, fatigue, low self-esteem, feelings of guilt and self-blame, and sleep disturbance (94,96,97,98). They often experience social isolation, phobias, feelings of vulnerability, fear, humiliation, grief, and loss of control (99,100). Survivors of sexual assault represent a disproportionate number of patients with chronic headaches and chronic pelvic pain (they have a lower pain threshold) and are more likely to have somatic symptoms that do not respond to routine medical treatment (97,101). Women with common gynecologic symptoms, such as dysmenorrhea, menorrhagia, and

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sexual dysfunction, are much more likely to have a history of sexual assault (102). If they have been forced to perform oral sex, they may have a dental phobia and avoid preventive dental care.

Survivors may develop posttraumatic stress disorder (PTSD), in which characteristic symptoms are exhibited following a psychologically traumatic event outside of normal human experience. Symptoms of PTSD include blunting of affect, denial of symptoms, intrusive re-experiencing of the incident, avoidance of stimuli associated with the assault, and intense psychological distress and agitation in response to reminders of the event (81,91). Women affected by PTSD are more likely to commit suicide. The cognitive sequelae include flashbacks, nightmares, disturbances in perception, memory loss, and dissociative experiences (103). These women may not be able to tolerate pelvic examinations and may avoid seeking routine gynecologic care because these examinations may remind them

of the sexual abuse they experienced as children. However, they are more likely to use the medical care system for nongynecologic concerns (104). Women with PTSD are at greater risk for being overweight and having gastrointestinal disturbances (89).

Rape

Although the legal definition of sexual assault may vary from state to state, most definitions of rape include the following elements:

- **The use of physical force, deception, intimidation, or the threat of bodily harm**
- **Lack of consent or inability to give consent because the survivor is very young or very old, impaired by alcohol or drug use, unconsciousness, or mentally or physically impaired**
- **Oral, vaginal, or rectal penetration with a penis, finger, or object**

The National Women's Study provides the best statistics available about the incidence of forcible rape in the United States (99). This study revealed that 13%, or **one of eight adult women, are survivors of at least one completed rape during their lifetime**. Of the women they surveyed, 0.7% had been raped during the past year, equaling an estimated 683,000 adult women who were raped during a 12-month period. Of the women surveyed, 39% were raped more than once. Most disturbing, however, is the finding that most rapes occurred during childhood and adolescence; 29% of all forcible rapes occurred when the survivor was younger than 11 years of age, and 32% occurred between the ages of 11 and 17 years. Indeed, "rape in America is a tragedy of youth" (99). Twenty-two percent of rapes occurred between the ages of 18 and 24 years, 7% between the ages of 25 and 29 years, and only 6% occurred when the survivor was older than 30 years of age. Although women of all ages and cultures are vulnerable to sexual assault, prisoners, adolescents, drug users, the elderly, those who experienced sexual assault as children, women in abusive relationships, and women with emotional and physical disabilities are at most risk (106).

There are many myths about rape. Perhaps the most common myth is that women are raped by strangers. In fact, **only about 20% to 25% of women are raped by someone they do not know. Most women are raped by a relative or acquaintance (9% by husbands or ex-husbands, 11% by fathers or stepfathers, 10% by boyfriends or ex-boyfriends, 16% by other relatives, and 29% by other nonrelatives)** (99). Although acquaintance rape may seem to be less traumatic than stranger rape, survivors of acquaintance rape often take longer to recover. Another common misconception about rape is that most survivors sustain serious physical or life-threatening injury. Sixty percent of rape

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survivors report some physical injury. General body injury is more than twice as common as genital and anal injury (107). Serious injury is rare, occurring 4% of the time, although almost half of the rape survivors report being fearful of serious injury or death during the assault (99). The most common genital injuries from a sexual assault are vaginal lacerations resulting in bleeding and pain. Intraperitoneal extension of a vaginal laceration or damage to the anal mucosa is rare (108). Common nongenital injuries in survivors include cuts, bruises, scratches, broken bones and teeth, and knife or gunshot wounds (109). About 0.1% of sexual assaults result in death. Common causes of death during a sexual assault include mechanical asphyxiation, trauma, lacerations, drowning, and gunshot wounds (108).

There are at least four types of rapists (110):

- **Opportunist rapists (30%) exhibit no anger toward the women they assault and usually use little or no force.** These rapes are impulsive and may occur in the context of an existing relationship (date or acquaintance rape). The highest incidence of acquaintance rape is among women in the twelfth grade of high school and in the first year of college (111). As many as half of college women report date rape. Many of these women may have been unable to give consent because they are impaired by alcohol or so-called date rape drugs (Rohypnol and gamma-hydroxy butyrate [GHB]). Date rape may have even greater psychological consequences than rape by a stranger because it involves a violation of trust (108).
- **Anger rapists (40%) usually batter the survivor and use more physical force than is necessary to overpower her.** This type of sexual assault is episodic, impulsive, and spontaneous. An anger rapist often physically assaults his victim, sexually assaults her, and forces her to perform degrading acts. The rapist is angry or depressed and is often seeking retribution—for perceived wrongs or injustices he imagines have been done to him by others, especially women. He may victimize the very young or the very old.
- **Power rapists (25%) do not intend to physically harm their victim but rather to possess or control her to gain sexual gratification.** However, a power rapist may use force or the threat of force to overcome his victim. These assaults are premeditated and repetitive, and they may increase in aggression over time. The rapist is usually anxious and may give orders to his victim, ask her personal questions, or inquire about her response during the assault. This assault may occur over an extended period while the victim is held captive. These rapists are insecure about their virility and are trying to compensate for their feelings of inadequacy and low self-esteem.
- **Sadistic rapists (5%) become sexually excited by inflicting pain on their victim.** These rapists may have a thought disorder and often exhibit other forms of psychopathology. This type of assault is calculated and planned. The victim is often a stranger. The rape may involve bondage, torture, or bizarre acts and may occur over an extended period of time. The victim often suffers both genital and nongenital injuries and may be murdered or mutilated. Other rapists may act out of impulse, as when they encounter a victim during the course of another crime such as burglary. Some rapists believe they are entitled to their victim, as in acquaintance rape or father–daughter incest (112). A consistent finding among all types of rapists is a lack of empathy for the survivor.

Even when sexual assaults are reported (only 16% of rapes are ever reported to the police), few rapists are arrested, and even fewer are brought to trial and convicted. Fewer than 1% of rapists ever serve a prison term (110,113).

Successful prosecution

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of rapists is often dependent upon the extent of the survivor's injuries and the completion of a detailed forensic examination (114). Many women do not report the assault to the police because they are concerned about their name being disclosed by the news media, fear retaliation from the perpetrator, are afraid they will not be believed, or do not trust the judicial process (115). Assault is more likely to be repeated if survivors in abusive relationships do not seek medical care, report the incident to police, or seek an order of protection (85).

Only 26% of rape survivors seek medical attention after an assault (85). Women are more likely to immediately seek treatment after sexual assault if weapons were involved, serious physical injury occurred, or physical coercion or confinement was used in the assault (116). Many rape survivors do not inform their physicians about the assault and may never volunteer information about the assault unless they are directly asked. Therefore, when obtaining a medical history, physicians should routinely ask, "Has anyone ever forced you to have sexual relations?"

Effects of Rape

Following sexual assault, women have many concerns, including pregnancy, STDs (including human immunodeficiency virus [HIV] infection), being blamed for the assault, having their name made public, and having their family and friends find out about the assault. The initial reactions to sexual assault may be shock, numbness, withdrawal, and possibly denial. It is difficult to predict how any assaulted individual will react. Despite their recent trauma, women presenting for medical care may appear calm and detached (114).

The **rape trauma syndrome** is a constellation of physical and psychological symptoms, including fear, helplessness, disbelief, shock, guilt, humiliation, embarrassment, anger, and self-blame. The acute, or disorganization, phase of the syndrome lasts from days to weeks. Survivors may experience intrusive memories of the assault, blunting of affect, and hypersensitivity to environmental stimuli. They are anxious, do not feel safe, have difficulty sleeping and eating, and experience nightmares and a variety of somatic symptoms (112,117,118). They may fear that their assailant will return to retaliate or rape them again.

In the weeks to months following the sexual assault, survivors often return to normal activities and routines. They may appear to have dealt successfully with the assault, but they may be repressing strong feelings of anger, fear, guilt, and embarrassment. In the months following the assault, survivors begin the process of integration and resolution. During this phase, they begin to accept the assault as part of their life experience, and somatic and emotional symptoms may decrease progressively in severity. However, the sequelae of rape are often persistent and long lasting (91). Over the long term, survivors may have difficulty with work and with family relationships. Disruption of existing relationships is not uncommon. Nearly half of the survivors lose their jobs or are forced to quit in the year following the rape, and half change their place of residency (100).

Table 11.8 Prophylactic Medications Following Sexual Assault

<i>Gonorrhea</i>	<i>Ceftriaxone</i> 125 mg IM or <i>Ciprofloxacin</i> 500 mg PO or <i>Spectinomycin</i> 2 g IM
<i>Chlamydia</i>	<i>Azithromycin</i> 1 g PO or <i>Doxycycline</i> 100 mg PO bid × 7 days or <i>Erythromycin</i> 500 mg PO qid × 7 days
<i>Trichomoniasis and bacterial vaginosis</i>	<i>Metronidazole</i> 2 g PO
<i>Hepatitis B</i>	Vaccine 1.0 mL IM. Repeat in 1 and 6 months.
<i>Tetanus (if indicated)</i>	Td 0.5 mL IM
<i>HIV</i>	<i>Zidovudine</i> 300 mg and <i>Lamivudine</i> 150 mg (<i>Combivir</i>), PO bid for 28 days. Addition of protease inhibitor should be considered for high-risk exposures.

Pregnancy

Plan B (levonorgestrel 0.75 mg) 2 tablets immediately **or**
Ovral 2 tablets immediately, repeat in 12 hours **or**
 35 µg combination birth control pill, 4 tablets
 immediately,
 repeat in 12 hours **or**
Mifepristone 10 mg as a single dose **or**
 Placement of a copper IUD

IM, intramuscularly; PO, by mouth; bid, twice a day; qid, four times a day; Td, tetanus and diphtheria; IUD, intrauterine device.

Examination and Treatment

The responsibilities of physicians providing immediate treatment for sexual assault survivors are listed in Table 11.8. **Because of the legal ramifications, consent must be obtained from the patient before obtaining the history, performing the physical examination, and collecting evidence. Documentation of the handling of specimens is especially important, and the chain of evidence for collected material must be carefully maintained. Everyone who handles the evidence must sign for it and hand it directly to the next person in the chain. The patient should be interviewed in a quiet and supportive environment by an examiner who is objective and nonjudgmental. Support personnel and patient advocates, such as family, friends, or, if available, a counselor from a rape crisis service, should be encouraged to accompany the patient. It is important not to leave the survivor alone and to give her as much control as possible over the**

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examination. To provide useful forensic information, the examination should be performed as soon as possible after the incident occurred.

The history should include the following information:

- **A general medical history and a gynecologic history must be obtained**, including last menstrual period; prior pregnancies; past gynecologic infections; tetanus status; history of liver disease, thrombosis, or hypertension (possible contraindications to emergency contraception with estrogens); contraceptive use; prior sexual assault; and last consensual intercourse before the assault.
- **It is important to ascertain whether the survivor bathed, douched, used a tampon, urinated, defecated, brushed her teeth, or changed her clothes after the assault.**
- **A detailed description of the sexual assault should be obtained**, including the place, time, and date of the assault; number of assailants; use of drugs or alcohol in relation to the assault; loss of consciousness; use of weapons, threats, and restraints; and any physical injuries that may have occurred.
- **A detailed description of the type of sexual contact must be obtained**, including whether vaginal, oral, or anal contact or penetration occurred; insertion of a foreign object with a description of the object; whether the assailant used a condom; and whether there were other possible sites of ejaculation, such as the hands, clothes, or hair of the survivor.

The emotional state of the survivor should be observed and recorded.

The physical examination serves to detect, evaluate, and treat all injuries and to collect forensic evidence (119). The survivor should undress while standing on clean examination

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table paper to catch any hair or fibers falling from her clothing. All of her clothing should be placed by the survivor (to avoid contamination) in individually labeled paper bags, sealed, and given to the proper authorities. Wet or damp clothing should be air dried before packaging because DNA evidence degrades quickly if it is moist (106). During the physical examination, the degree of injury to the survivor should be assessed, and any injuries should be documented for use as evidence. The nature, size, and location of all injuries should be carefully documented, using photographs or body charts (traumagram) if possible. Nongenital injuries occur in 20% to 50% of all rapes, so it important to examine the entire body (119,120).

The most common injuries are bruises and abrasions of the head, neck, and arms (112), as well as genital injuries accompanied by bleeding and pain. Hair and skin should be examined for dirt, foreign material, dried blood, and dried semen (119). Ruptured blood vessels in the retina may be the result of trauma from choking. If oral penetration has taken place, injuries of the mouth and pharynx may occur (121). Injury to the oral cavity, including a torn frenulum, broken teeth, trauma to the uvula, and injuries of the hard and soft palate, are related to forced fellatio.

The most common genital findings are erythema and small tears of the vulva, perineum, and introitus. A Foley catheter, placed in the distal vaginal vault and then inflated, allows for full visualization of hymenal injuries (105). There may be bleeding, mucosal tears, erythema, or a hematoma noted around the rectum if penetration has occurred. Identification of small lacerations of the genitalia or rectum may be aided by colposcopy or by staining with toluidine blue, which has an affinity for the nuclei of exposed submucosal cells (120,121,122,123). Toluidine blue should be applied before the speculum examination, as insertion of the speculum itself can cause small lacerations and false-positive results. Toluidine blue is also spermicidal and should not be applied until all forensic evidence is collected (122). Bite marks are not uncommon and frequently are found on the breasts or genitalia. Foreign bodies may be found in the vagina, rectum, or urethra.

Samples should be obtained from any sites of contact (vagina, rectum, or mouth) and tested for gonorrhea and chlamydia. A vaginal wet prep examination should be performed for evidence of trichomonas. A urine or serum pregnancy test should be performed, as well as baseline testing for syphilis, hepatitis B, and HIV.

Evidence must be properly collected for legal purposes according to the following procedures:

- **Examination of the patient with a Wood light may help identify semen,** which will fluoresce blue-green to orange. Areas of fluorescence should be swabbed with a cotton-tipped applicator moistened with sterile water, then air dried and submitted as evidence. Swabs of the skin, vagina, mouth, and rectum may be obtained to test for the presence of sperm or semen.
- **A Pap test may also be useful to document the presence of sperm.**
- **A sample of the vaginal secretions should be obtained for examination for motile sperm, semen, or pathogens.** Motile sperm in the vagina indicate ejaculation occurred within

6 hours. Nonmotile sperm can be found in the cervical mucus for as long as 1 week. If ejaculation has occurred in the mouth, seminal fluid will be rapidly destroyed by salivary enzymes (108). If the survivor reports an anal assault, specimens can be obtained by washing the rectal vault with 10 mL of normal saline injected with a red rubber catheter. Allow the saline to stand for several minutes, then aspirate the rectal fluid and submit as evidence.

- **Vaginal secretions should also be collected for DNA fingerprinting and to test for the presence of seminal contents**, including acid phosphatase, p30 protein (specific to the prostate), seminal vesicle-specific antigen, and ABO antigens (83).
- **The survivor's pubic hair should be combed over a sheet of paper in an attempt to obtain pubic hair from the assailant.** Both the comb and the pubic hair should be submitted as evidence.
- **Fingernail scrapings from the survivor should be collected** and evaluated for evidence of trace fibers or the assailant's blood, hair, or skin. This evidence may also be used for DNA fingerprinting.
- **Saliva should be collected from the survivor** to document whether she is a secretor of major blood group antigens (80% of the population are secretors). If the patient is not a secretor and blood group antigens are found in vaginal washings, the antigens are probably from the semen of the assailant (83).

Treatment of sexual assault survivors should be directed to prevention of possible pregnancy and provision of prophylactic treatment for STDs (Table 11.8). About 5% of fertile rape survivors will become pregnant as a result of the rape (124). Options include awaiting the next expected menses, repeating the serum pregnancy test in 1 to 2 weeks, and using emergency (postcoital) contraception. If the patient desires emergency contraception, a preexisting pregnancy can usually be ruled out by performing a sensitive human chorionic gonadotropin assay. Pregnancy prophylaxis can be provided by several different regimens (125,126) (see also Chapter 10):

- **Administration of one tablet containing 0.75 mg of *levonorgestrel* followed by a second tablet 12 hours later (Plan B). A single 1.5-mg dose of *levonorgestrel* is just as effective as the two-dose regimen and is the preferred method of emergency contraception** (126)
- **Immediate administration of two tablets of a combination oral contraceptive (each containing 50 µg of *ethinyl estradiol* and 0.5 mg *norgestrel*, i.e., *Ovral* birth control pills) followed by two more tablets 12 hours later (Yuzpe regimen)**
- **Four tablets of a combination birth control pill containing 35 µg of *ethinyl estradiol* and a progesterone followed by four more tablets 12 hours later**
- ***Mifepristone* as a single 10 mg dose** (127)

Placement of a copper-containing intrauterine device

These regimens are highly effective if administered within 120 hours after the sexual assault (126,128). However, the sooner the medications are taken, the more effective they are. Most regimens have a failure (pregnancy) rate of about 1.5%. Some patients experience nausea and vomiting when given emergency contraception containing estrogen, which can be controlled with an antiemetic agent such as *promethazine* (12.5 mg every 4–6 hours). Single-dose *levonorgestrel* is more effective and is associated with fewer side effects than the Yuzpe regimen, and is the method of choice for emergency contraception. Emergency contraception has a small failure rate but poses little teratogenic risk if the pregnancy continues (129). Most women who take emergency contraception usually experience their next menstrual period within 3 days of the expected date. However, women using *mifepristone* for emergency contraception may experience delayed onset of the subsequent menstrual period (127). Emergency contraception may delay but not prevent ovulation; for this reason, patients receiving emergency contraception should be encouraged to use contraception if further coital episodes occur during the cycle.

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The risk of acquiring an STD from a rape is difficult to assess because the prevalence of preexisting STDs is high (43%) in rape survivors (130,131,132). **However, the risk is estimated as follows: gonorrhea, 6% to 12%; trichomonas, 12%; chlamydia, 2% to 12%; syphilis, 5%.**

Because it is difficult to differentiate between a preexisting STD and a newly contracted one attributable to a sexual assault, prophylaxis should be offered to all survivors. This is especially important because most sexual assault patients do not return for follow-up appointments (118). Prophylaxis should cover infections with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, trichomonas, bacterial vaginosis, incubating syphilis, and HIV. Current recommendations include (131,133):

- *Ceftriaxone*, 125 mg intramuscularly for the treatment of gonorrhea (if the patient is allergic to cephalosporins, *spectinomycin*, 2 g intramuscularly, or *ciprofloxacin*, 500 mg orally, may be used), PLUS:
- A single dose of 1 g of *azithromycin* orally or 100 mg of *doxycycline* orally twice a day for 7 days for treatment of chlamydia (if the patient is pregnant at the time of the assault, *erythromycin* 500 mg orally four times a day for 7 days may be substituted for *doxycycline*), PLUS:
- A single dose of 2 g of *metronidazole* orally for the treatment of trichomoniasis and/or bacterial vaginosis

Hepatitis B vaccination should be offered if the sexual assault survivor has experienced vaginal, oral, or anal penetration. Hepatitis B is 20 times more infectious than HIV during intercourse (83). Vaccination is recommended at the time of the initial evaluation. Subsequent doses are provided 1 month and 6 months after the first dose is administered. It is not necessary to treat the patient with hepatitis B immune globulin (133).

Tetanus prophylaxis (0.5 mL intramuscularly) should also be administered if indicated. Conversion of HIV through sexual assault, although reported, is low and similar to conversion from occupational exposure (0.1% to 0.3% per episode) (134). The probability of transmission depends on the type of assault, presence of trauma and bleeding, site of ejaculation, HIV viral load in the ejaculate, presence of a concomitant STD or ulcerative lesions in the assailant or survivor, and the community prevalence of HIV/acquired immune deficiency syndrome (120,134). Factors to consider when discussing HIV postexposure prophylaxis with patients include the likelihood of exposure to the virus, the risks and benefits of treatment, the interval between the sexual assault and the initiation of therapy, and the patient's desire to be treated. All survivors of unprotected vaginal or anal sexual assault presenting within 72 hours should be offered HIV prophylaxis unless the assailant is known to be HIV negative (135). Treatment should be initiated as soon as possible. The usual regimen is Combivir or its equivalent (300 mg *zidovudine* [AZT] and 150 mg *lamivudine* [3TC]) administered twice daily for 4 weeks). Administration of a protease inhibitor (*nelfinavir*, five 250 mg tablets twice a day for 28 days) should be considered for high-risk exposures, such as when the assailant is known to be HIV infected. Side effects of HIV prophylaxis include nausea, malaise, headache, and anorexia. About 33% of survivors who elect to take antiviral medication discontinue therapy prematurely (134). Patients should be aware that the efficacy of prophylactic treatment for HIV after sexual assault is unknown and they will have to be carefully monitored if they initiate treatment with antiretroviral medication.

If prophylactic treatment for gonorrhea, chlamydia, trichomonas, and bacterial vaginosis is not given, the survivor should return in 2 weeks for repeat testing for STDs and pregnancy. If the initial serologic test results were

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negative, repeat serologic tests for syphilis, hepatitis B, and HIV should be performed at 6, 12, and 24 weeks after the assault.

Ongoing supportive counseling for the patient should be arranged, and the patient should be referred to a sexual assault center or a therapist who specializes in the treatment of sexual assault survivors.

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12

Common Psychiatric Problems

Nada Logan Stotland



- **Accurate diagnosis is the key to successful treatment.**
- **Most psychotropic medications appear to be relatively safe to use during pregnancy and lactation, but because studies are appearing at a rapid rate, it is essential to consult the latest literature before making clinical decisions. Withdrawal of successful psychotropic treatment is not indicated.**
- **Personality disorders and somatizing disorders can rarely be cured, but informed management can greatly decrease the suffering of the patient, the drain on the family, and the frustration of the health care team.**

Domestic violence and other unfortunate social circumstances are major risk factors for psychiatric illness.

Some women are vulnerable to mood symptoms at times of hormonal change. However, menopausal hormone levels are not correlated with depression, and premenstrual syndrome should not be diagnosed without 2 months of prospective daily ratings.

Psychiatric problems are a central or complicating factor for many patients who seek care on an outpatient basis (1,2). Psychiatric diagnoses are extremely common and account for considerable morbidity and mortality in the general population (3). Despite their prevalence, however, psychiatric disorders are often undiagnosed or misdiagnosed (4,5,6,7). **Clinical depression affects up to one fourth of women during their lives (8,9,10), but an estimated 80% of the cases are neither diagnosed nor treated (11).** More than one half of the patients who commit suicide have seen a nonpsychiatric physician during the previous 3 months (12).

The Context of Psychiatric Conditions

Many gynecologists feel uncomfortable diagnosing and treating psychiatric illnesses for a number of reasons. The practice of gynecology is demanding. Patients with psychological problems can evoke negative reactions in physicians (Table 12.1). In the past, gynecologists have found it difficult to use psychiatric diagnostic systems because they were based on theories of unconscious motivation and conflict. New systems for the diagnosis of psychiatric disorders are reliable and valid and can be systematically applied, and many psychiatric treatments are specific and effective. By incorporating these management strategies into practice, gynecologists can play a major role in improving the health and well-being of their patients.

Table 12.1 Practitioners' Negative Reactions Toward Patients with Psychiatric Problems

1. Social stigma attached to psychiatric diagnoses, patients, and practitioners.
2. Belief that individuals with psychiatric disorders are weak, unmotivated, manipulative, or defective.
3. Belief that the criteria for psychiatric diagnoses are intuitive rather than empirical.
4. Belief that psychiatric treatments are ineffective and unsupported by medical evidence.
5. Fear that patients with psychiatric problems will demand and consume inordinate and limitless time from a medical practice.
6. Precipitation in others, including doctors, of feelings that are complementary to the strong and unpleasant emotions experienced by patients with psychiatric disorders.

7. Gynecologists' own uncertainty about their skills at psychiatric diagnosis, referral, and treatment.
8. Failure to view psychiatric problems as legitimate grounds for medical attention.

Psychiatric Assessment

In the past, the diagnosis of psychiatric disorders was based partially on hypotheses about a patient's unconscious psychological conflicts, which cannot be verified (13). **Current psychiatric diagnosis, as codified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, produced and published by the American Psychiatric Association, is based on empirical, valid, and reliable evidence.** The DSM-IV yields reliability comparable to that of diagnostic systems used in other areas of medicine, and its diagnoses strongly correlate with response to treatment. The criteria in DSM-IV are the basis for the diagnostic entities described in this chapter (see also Chapter 1). The new edition, DSM-IV-TR, differs only in the explanations of some of the diagnoses and not in the diagnostic criteria themselves. **The DSM-IV-PC is a special edition designed for the primary care provider. This volume is organized by initial signs and symptoms rather than psychiatric categories and uses algorithms and decision trees to facilitate the diagnostic process.** Accurate diagnosis is absolutely critical to successful management, whether care is provided by a gynecologist or through referral to a mental health expert.

Approach to the Patient

Although diagnostic criteria list signs and symptoms, the interaction with a patient should not be reduced to a series of rapid-fire questions and answers. **A wealth of valuable information can be obtained from the patient's spontaneous description of her concerns and from her responses to the physician's open-ended questions** (14). A patient who is encouraged to speak for several minutes before being asked to respond to specific questions will reveal information that is useful, even vital, to her care: a thought disorder, a predominant mood, abnormally high anxiety, a personality style or disorder, and attitudes toward her diagnosis and treatment. Such information may emerge only much later, or not at all, in a question-and-answer format (15,16). **It is critical that the gynecologist neither jumps to diagnostic conclusions nor proceeds directly to therapeutic interventions.**

One study revealed that many primary care physicians, feeling that they had too little time or training to assess psychological symptoms, tended to minimize verbal interactions with patients and to rely on the prescription of psychotropic medications (17). Allowing a few moments for open-ended discussion does not mean that the physician and the other patients awaiting care are to be held hostage by an overly talkative patient, however. The clinician can tell the patient with multiple, detailed symptoms how much time is available for

the current appointment, invite her to focus on her most pressing problem, and offer a future appointment to continue the account.

Psychiatric Referral

Many gynecologists consider referral to a mental health professional, particularly a psychiatrist, to be a delicate matter. The first question is when to refer, followed by how to refer and to whom. Most mild psychiatric disorders are treated by nonpsychiatric physicians (18), who often prescribe antidepressants and anxiolytic medications. At the same time, however, psychiatric disorders often are overlooked, misdiagnosed, or mistreated in primary care practice. The following factors determine the decision to refer:

- The nature and severity of the patient's disorder
- The expertise of the gynecologist
- The time available in the gynecologic practice
- The patient's preference
- The gynecologist's degree of comfort with the patient and the disorder
- The availability of mental health professionals

Patients who are suicidal, homicidal, or acutely psychotic should be referred to a psychiatrist. Patients also should be referred for psychiatric evaluation when the diagnosis is not clear or when the patient fails to respond to initial treatment by the primary provider. For many patients, the gynecologist can resume responsibility for ongoing care after an initial or periodic assessment by a psychiatrist.

How to Refer?

Some clinicians fear that patients will be insulted, alienated, or alarmed by a psychiatric referral. Following are techniques that decrease the discomfort of both the gynecologist and the patient and enhance the likelihood of a successful referral (19). The referral should be explained on the basis of the patient's own signs, symptoms, and level of distress. For a patient suffering from clinical depression, for example, this might be difficulty sleeping, loss of appetite, or lack of energy. For a patient with an anxiety disorder, it might be

paranoia, episodes of crying, or forgetfulness. For a patient with mild Alzheimer's disease, it might be forgetfulness or frightening episodes in which she finds herself in a neighborhood she does not recognize. With the advent of treatments that may slow dementia, these referrals are easier and more meaningful because there is now some hope for effective intervention.

When a somatizing (psychosomatic) disorder is suspected, the gynecologist should emphasize the difficulty of living with symptoms in the absence of a definitive diagnosis and treatment rather than the hypothesis that the symptoms have a psychological basis:

- *"It is very stressful to be suffering while we can't pinpoint the problem. I would like you to see one of our staff who specializes in helping people cope with these difficult situations."*
- *"It must be difficult to function when you have been so sickly all your life, have seen so many doctors, have had so many diagnostic tests and medical treatments, and still don't have an answer or feel well."*

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It is counterproductive to convey the idea that because the diagnostic process has not revealed a specific disorder, the problem must be "in the patient's head." It alienates the patient, and in any event, it is never possible to rule out an organic cause with absolute certainty.

Although suicidal and homicidal behaviors are absolute indications for referral, many physicians fear that questioning patients about these behaviors will provoke them. That is not the case (12). An open discussion of impulses to hurt oneself or someone else helps the patient to regain control, recognize the need for mental health care, or agree to emergency interventions such as psychiatric hospitalization, whereas avoiding the subject intensifies the patient's feelings of isolation. The management of suicidal behavior is addressed later in this chapter in the section on mood disorders.

Likewise, the possibility of psychosis need not be avoided. Most patients with psychotic disorders have had previous experience with psychiatric referral. Their psychotic symptoms are often distressing, so treatment is an appealing option. They generally can discuss hallucinations and delusions quite matter-of-factly. The rare patient who comes to a gynecologist in the midst of a first episode of psychosis is likely to be frightened by her symptoms and willing to accept expert consultation.

Despite increasing public sophistication about mental illnesses and psychiatric care, some patients believe that any mention of mental health intervention implies either that they are "crazy" or that the referring physician is convinced that their physical symptoms are imaginary or feigned. The gynecologist may wish to state explicitly that this is not the case. Again, making the real reason for the referral clear and founded in signs and symptoms obvious to the patient

will nearly always allay anxiety over a psychiatric referral.

It is not acceptable to refer a patient to a psychiatrist without informing and asking her in advance and obtaining her consent unless she is acutely psychotic, functionally incompetent, or in the throes of a suicidal or homicidal emergency. Even under those circumstances, it is highly preferable to be straightforward. A referral that begins with an unexpected clinical encounter with a psychiatrist is unfair to the psychiatrist and the patient and is unlikely to result in a satisfactory outcome.

To allay any concern a patient may have that a mental health referral is an indication of the gynecologist's disdain or disinterest, and to promote good patient care in general, the referring gynecologist should make it clear to the patient that he or she will remain involved in her care. The mental health professional should be introduced as a member of the health care team, and the gynecologist should ask the patient to call after the mental health appointment to report on how it went. The patient should be given a follow-up appointment with the gynecologist at the time of the referral.

Where to Refer: Which Mental Health Professional?

Mental disorders are treated by social workers, psychologists, members of the clergy (often the first to be consulted), and various kinds of counselors as well as by psychiatrists. The distinctions between mental health professionals are neither generally well known nor understood by the lay public or even medical professionals. The criteria for membership in each profession can vary by region and institution. Social workers and psychologists can receive degrees at the bachelor, master, or doctoral level. In some states, licensure is required; generally, social workers require a master's degree and psychologists receive a doctoral degree, in addition to supervised clinical experience, to qualify for licensure. The category of counselor includes a wide variety of practitioners, such as marriage counselors, pastoral counselors, school counselors, and family counselors. The training of social workers may focus on social policy, institutional care, psychosocial aspects of medical illness, or individual treatment.

Practitioners of all these disciplines may or may not be trained in psychotherapy. For a patient whose symptoms do not meet criteria for a major psychiatric disorder and who is able to eat, sleep, and carry out her regular duties, supportive psychotherapy provided by a trained mental health professional may suffice. Supportive psychotherapy calls on a patient's existing coping mechanisms to combat a stressful situation. Doctoral-level psychologists and neuropsychologists also can perform testing that can be helpful in establishing a diagnosis. Such testing is especially useful in identifying and localizing brain pathology and in defining intelligence levels. Undiagnosed cognitive deficits may contribute to noncompliance with gynecologic care as well as other problems.

Trained social workers are often knowledgeable about community resources for patients and their families and about the impact of gynecologic diseases and

treatments on them. Self-help or professionally led therapy groups can be helpful for patients reacting to gynecologic problems such as infertility or malignancy. Participation in a supportive group was said to lengthen the survival time and improve the quality of life for some patients with cancer (20,21,22,23,24,25,26), although there is some controversy about this assertion.

Psychiatrists are the only medically trained mental health professionals. They play a particularly important role in resolving diagnostic dilemmas, especially when questions arise about the psychological or behavioral manifestations of medical illness and pharmacologic treatment, and when a medical understanding of the gynecologic condition and treatment is essential to the care of the patient. Of all mental health professionals, only psychiatrists have been licensed to prescribe psychoactive medications and other biologic interventions as well as provide psychotherapy. Currently, the legislatures of New Mexico and Louisiana have conferred prescribing rights on doctoral-level psychologists with additional training but have not defined what the additional training or the limits of the prescribing authority, if any, will be. Psychiatrists continue to treat the most seriously ill patients and take ultimate responsibility for psychiatric emergencies.

In light of the frequent occurrence of psychiatric problems in gynecologic practice, it is worthwhile for the gynecologist to develop an ongoing relationship with one or more local mental health professionals. The state psychiatric society may have a list of subspecialists in "consultation liaison" psychiatry; this is a subspecialty recently accepted by the American Board of Psychiatry and Neurology. Many psychiatrists who have not had fellowship training offer consultative services. The availability of familiar and trusted resources enhances the likelihood that problems will be identified and addressed. An ongoing relationship with a mental health professional also allows the gynecologist to familiarize that professional with relevant developments in gynecology. **It is important to keep up-to-date information on local suicide prevention hotlines and other kinds of resources for battered women and for mothers who may pose a danger to their children.** Local laws may require that physicians report to the authorities their knowledge of mothers in this situation.

Specific Disorders

Whenever a patient's thinking, emotions, or behaviors cause concern, the gynecologist should first consider a nonpsychiatric medical disorder or a reaction to prescribed or illicit drugs. Psychiatric disorders frequently coexist with these conditions.

Manic-Depressive Disorders

Mood is the emotional coloration of a person's experience. **Mood may be pathologically elevated (mania) or lowered (depression) or may alternate between the two (bipolar or manic-depressive disorder)** (26). Mood disorders are different from, but frequently confused with, the inevitable ups and downs of everyday life, such as the reactions to

difficult situations, including gynecologic conditions. In the English language, *depression* is used to describe both a transient mood and a psychiatric disorder. Because of this confusion, both patients and their loved ones become frustrated when well-meaning attempts to reason with them, distract them, or do thoughtful things for them fail to influence their protractedly disturbed moods.

Mania is characterized by the following behavior:

- **Elevated mood, with euphoria or without irritability**
- **Grandiosity**
- **Pressured, accelerated speech and physical activity**
- **Increased energy**
- **Decreased sleep**
- **Reckless and potentially damaging behaviors, such as wild expenditures and promiscuity**

Mania can be acute or subacute (hypomania). Hypomania can produce self-confidence, ebullience, energy, and productivity that are the envy of others, making the patient reluctant to relinquish this mood for treatment. It can therefore be particularly difficult to arrest the condition before it progresses to full-blown mania. Acute mania is a life-threatening condition; without treatment, patients fail to maintain essential sleep and nutrition levels and literally exhaust themselves with frantic activity.

Depression

The overall lifetime prevalence of affective disorders is 8.3%; the 6-month prevalence is 5.8%. **During the reproductive years, depression is 2 to 3 times more common in women than in men** (26,27,28,29,30,31,32). The highest incidence of depression is in the age group of 25 to 44 years, but depression occurs in every age group, from toddlers to the aged. Women have a lifetime risk of 10% to 25% and a point prevalence of 5% to 9% (33,34,35,36). Depression is the single most common reason for psychiatric hospitalization in the United States. **As many as 15% of individuals with severe depressive disorders eventually commit suicide.** Depression is a recurrent disorder; of those

who experience a major depressive episode, 50% have a second one. Of these, 70% have a third, and the incidence continues to increase with each subsequent episode. It is difficult to know whether the incidence of depression has increased over recent years because diagnostic criteria in the past were vague.

Because women's roles in society have changed a great deal over the last few decades, there is a temptation to attribute the higher rate of depression to women's work outside the home. There is no evidence that employment outside the home increases women's vulnerability to depression, although the need to carry out multiple roles in the absence of adequate social support can be stressful (37,38,39).

Depression is characterized by the following behavior:

- **Sad mood or irritability**
- **Hopelessness**
- **Helplessness**

- **Decreased ability to concentrate**
- **Decreased energy**
- **Interference with sleep, generally with early awakening, inability to return to sleep, and failure to feel rested; atypically, with increased sleep**
- **Decreased appetite and weight; atypically, increased food intake**
- **Withdrawal from social relationships**
- **Inability to enjoy previously gratifying activities**
- **Loss of libido**
- **Guilt**

Retardation of psychomotor skills or agitation

-

Thoughts of death or suicide

The patient who has five or more of the signs and symptoms of depression for most of each day for 2 weeks or more fulfills the criteria for the diagnosis of clinical depression. Depression may be acute or chronic (dysthymic disorder), and it can be caused by genetic, neurophysiologic, and environmental factors. Trauma in early life plays a role. Serotonin is a major mediator. Depression can improve with effective treatment, whether pharmacologic or psychotherapeutic, or spontaneous recovery. The average duration of a major depressive episode is approximately 9 months.

Depression may be precipitated by an adverse life event such as an interpersonal loss, economic reversal, or serious illness (40,41). When there is an identifiable precipitant, there is a danger that the depression will be written off as the inevitable reaction to the event rather than considered properly as a complication, similar to infection or pneumonia that requires active treatment. When a patient's symptoms meet criteria for the diagnosis, treating the depression will not only relieve symptoms, but also make her much more able to cope with the precipitating situation (42). Concomitant gynecologic or other medical illness can cause signs and symptoms similar to those of depression—loss of energy, sleep, and appetite—but does not cause guilt, hopelessness, or helplessness (43). These observations are helpful in differentiating depression from the malaise associated with other disease states.

Gynecologic Issues

The incidence of depression peaks, and the sex difference prevails, during the reproductive years (44). Connections between female reproductive functions and mood changes have been posited for centuries. When it first became possible to determine circulating hormone levels, researchers expected to find specific relationships between psychological and physiological changes. These expectations have been uniformly discounted. **There is no serum hormone level associated with premenstrual dysphoria, postpartum depression, or depression at menopause** (45). There is a subgroup of women who are vulnerable, not to absolute circulating hormone levels, but to hormonal changes (46,47,48,49). There is a correlation between the degree of hormonal change, pre- and postpartum, and the incidence of postpartum mood disorder. Women who are vulnerable to hormonal changes may experience severe premenstrual mood symptoms, postpartum depression, and, possibly, depression in association with hormonal influences such as hormonal contraceptive methods, menopause, and hormone treatments (50).

Premenstrual Syndrome

Depending on the methodology used to gather the data, most women report mood and behavioral changes associated with the menstrual cycle: premenstrual syndrome, or PMS.

An estimated 3% to 5% of ovulating women suffer from symptoms so marked that they qualify for a diagnosis of premenstrual dysphoric disorder (PMDD) (51,52,53).

PMDD is described in DSM-IV-TR. Provisional diagnostic criteria are provided to standardize research:

In most cycles over the past year, the patient has had at least five of the following symptoms for most of the time during the premenstrual week, with symptoms remitting completely in the postmenstrual week:

- **Depressed mood, hopelessness, self-deprecation**
- **Anxiety, tension**
- **Affective lability**
- **Anger, irritability, interpersonal conflict**
- **Decreased interest in usual activities**
- **Difficulty concentrating**
- **Decreased energy**
- **Appetite changes or cravings**
- **Changes in sleep**
- **Feeling overwhelmed or out of control**
- **Physical symptoms such as breast tenderness, headache, bloating**

The symptoms markedly interfere with work, family, or academic responsibilities; are not only exacerbations of another existing disorder; and are corroborated by at least 2 months of prospective daily ratings.

Premenstrual syndrome has been characterized by more than 100 different physical and psychological signs and symptoms, making it difficult to define scientifically. Methodological problems further complicate the situation; in the United States, the prevalence of attitudes linking the menstrual cycle to adverse mood and behavioral changes is so high that it skews women's perceptions, the way they report symptoms to researchers, and the factors to which they attribute negative feelings. No specific circulating hormone levels or markers are associated with premenstrual symptoms (54). **When prospective daily ratings are obtained systematically, the symptoms of most women who seek care for PMS are not related to the menstrual cycle** (55,56). Therefore, careful assessment is essential. Before the diagnosis of PMS or PMDD can be established, a woman must record symptom ratings daily for at least two full cycles. Records of emotions and behaviors should be kept separate from menstrual records to avoid confounding patients' perceptions. At the same time, the patient must be screened for other psychiatric disorders, including depression and personality disorders, and for domestic abuse and other life circumstances that may contribute to her psychological state (57).

No treatment for PMS has been validated by empirical studies (58). However, a number of **lifestyle changes and other benign interventions are effective for some patients with PMS** (59):

- **Elimination of caffeine from the diet**
- **Smoking cessation**

- **Regular exercise**
- **Regular meals and a nutritious diet**
- **Adequate sleep**
- **Stress reduction**

Stress reduction can be accomplished by reducing or delegating responsibilities, insofar as that is possible, and devoting part of every day to relaxation techniques such as yoga. Still, many women experience stress factors over which they have no control.

Several selective serotonin reuptake inhibitors (SSRIs) have proved effective for treatment of PMDD in clinical trials (60,61,62,63). Although SSRIs and all

other antidepressants require about 2 weeks of daily administration to achieve therapeutic effect, it appears that *fluoxetine* is effective for PMDD when taken in the usual daily doses for just the 1 to 2 weeks preceding menstruation. The medication has been packaged for this specific indication and dosage. It is thought that the mode of action of SSRIs when used in this fashion differs from that which alleviates major depression (63). Other medications for the treatment of PMS and PMDD are shown in Table 12.2. There has also been some interest in the role of oral contraceptives in management of PMDD (64).

Other Reproductive Events

Infertility is described by most women undergoing treatment as the most stressful event of their lives. Each unsuccessful treatment episode is experienced as the loss of a hoped-for pregnancy (65). The loss of a fetus or newborn also induces grief, with some of the same symptoms as depression. In general, depression is associated with guilt, whereas bereavement is not. However, women who lose pregnancies or infants often do feel guilty, regardless of whether these feelings are logically justified. Patients should not be pressed to "put the loss behind them" or expected to be "over it" within several months. Some feelings of sadness may persist for years. However, their sleep, appetite, and other vital functions and behaviors should begin to improve after a few weeks (66). Grief that not only persists, but interferes with normal functioning, is characterized as pathologic. Depression can complicate grief and should be treated (67).

There is no evidence that induced abortion causes clinical depression or any other negative psychiatric sequelae. Studies purporting to demonstrate negative sequelae fail to take into account the circumstances under which women often conceive unintended pregnancies and elect to terminate them—abuse, abandonment, poverty, rape, and incest—or the circumstances in which they occur—familial pressure or disapproval, clinic demonstrators (68).

Peripartum Psychiatric Disorders

The incidence of depression in women during their reproductive years is approximately 10%. The incidence of depression does not decrease during pregnancy; most postpartum depression is a continuation of antepartum depression (69,70,71). Although there are some cross-cultural variations currently under study, postpartum depression is found in around the globe (72). Risk factors include social isolation, lack of social supports, history of depression, and past or present victimization (73). Postpartum depression must be distinguished from the transitory, self-limited, and very common "baby blues," which are associated with changes in hormone levels and are better characterized as mood intensity and lability rather than depression. Mild depression can be managed with psychotherapy (74). Moderate to severe cases often require antidepressant medications (75). Electroconvulsive treatment acts rapidly and effectively, appears to be safe during and after pregnancy, and can be a life-saving option for the most severe cases (76). Treatment with artificial light may alleviate milder symptoms (77).

Table 12.2 Scientific Basis of Selected Medications Used to Treat PMS

<i>Treatment</i>	<i>Scientific Basis</i>	<i>Advantages</i>	<i>Disadvantages</i>	<i>Notes</i>
Alprazolam	Several double-blind, placebo-controlled, randomized crossover studies. Results were mixed. Placebo was as effective as alprazolam in some studies.	Oral medication appears to be more effective in alleviating depression and anxiety symptoms than physical symptoms.	Potential for dependence; requires tapering; drowsiness reported by many subjects; long-term effects unknown; safety during pregnancy unknown.	The studies involved highly selective groups of women. There was a high dropout rate in one of the positive studies. In one study that found <i>alprazolam</i> effective, 87% of the women had a history of major depression or an anxiety disorder. Different doses were used in the studies (0.75–2.25 mg); the standard effective dosage is unknown.
Fluoxetine (Prozac)	Several double-blind, randomized, placebo-controlled, crossover trials. All found fluoxetine effective.	Well tolerated; single daily oral dose. Significant decrease in psychic and behavioral symptoms.	Long-term effects unknown. Safety during pregnancy unknown. Appears less effective in controlling physical symptoms.	Trials involved very small, highly select groups of women. Duration of treatment did not exceed 3 months. All trials used 20 mg orally daily.
Gonadotropin-releasing hormone agonist	Several small, double-blind, randomized, placebo-controlled, crossover trials. Most patients experienced improvement.	Rapidly reversible; many patients report being virtually symptom-free during therapy.	Produces pseudomenopause; expensive; risk for osteoporosis, hypoestrogenic symptoms. Usually given for only short periods of time.	An add-back regimen of estrogen-progestin in addition to gonadotropin-releasing hormone agonist has been reported. If replicated, it may have potential for an effective, long-term treatment for premenstrual syndrome.

Spironolactone	Several double-blind, randomized, placebo-controlled trials. Mixed results.	May alleviate bloating and improve symptoms related to mood. Oral medication taken once or twice a day. Nonaddictive.	Effectiveness not proven consistently across studies.	<i>Spironolactone</i> is the only diuretic that has shown effectiveness in treating premenstrual syndrome in controlled, randomized trials. Method of action may be antiandrogen properties.
Vitamin B₆	Ten randomized double-blind trials. About one third of the trials reported positive results, one third reported negative results, and one third reported ambiguous results.		No conclusive evidence that vitamin B ₆ is more effective than placebo.	Doses ranged from 50 to 500 mg. Only one study involved more than 40 subjects. The large multicenter trial (N = 204) reported similar results for placebo and vitamin B ₆ .
PMS; premenstrual syndrome. From The American College of Obstetricians and Gynecologists. Committee Opinion. Washington, DC: ACOG, 1995, with permission.				

Although no agent can be declared perfectly safe for use during pregnancy and lactation, older SSRI agents have been well studied, yielding little or no evidence of adverse effects on the fetus or nursing infant (78,79,80). These agents also are used in the treatment of obsessive-compulsive disorder (81). Medication should not be stopped arbitrarily, nor should breastfeeding be prohibited. The withdrawal of antidepressant medication during

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pregnancy is very likely to result in postpartum depression; both antenatal and postnatal depression have demonstrable, long-term ill effects for mother and child (82,83,84,85,86,87,88). Recently, there has been concern about withdrawal syndromes in neonates whose mothers had been taking SSRIs (89). These concerns arise from anecdotal reports and do not include data about the number of births from which the reports emerged, nor about confounding variables. Some observers have recommended that pregnant women be withdrawn from SSRIs some days or weeks before delivery. However, delivery dates are often uncertain; maternal withdrawal might subject the fetus, rather than the newborn, to withdrawal symptoms; and the likelihood of postpartum depression, with its effects on both mother and infant, would be greatly increased. Researchers are currently exploring ways to prevent postpartum depression, but thus far nothing has proved effective (90,91).

Schizophrenia affects approximately 1% of persons worldwide. Since the deinstitutionalization of persons with severe and persistent mental illnesses several decades ago, most affected individuals live in the community. Often health care and other services

impregnation. Overall, the fertility of women with schizophrenia approximates that of matched populations. Schizophrenia is not an absolute contraindication to successful parenting, but there is considerable stigma against psychotic disorders, and patients may avoid prenatal care because they fear loss of custody (92,93). Older, atypical antipsychotic agents appear to be relatively safe for use during pregnancy (94). The care of these patients should be undertaken jointly by an obstetrician and a psychiatrist. The same is true of eating disorders and substance abuse, both of which pose substantial risks during pregnancy (95,96,97).

Decisions about the use of medications in pregnant and breastfeeding women should take into consideration the risks of untreated disease. Women whose partners or family members object to the use of medication should be encouraged to bring them to obstetric appointments to discuss the risks and benefits with professional health care providers so that the family is in agreement, if at all possible, and no one blames the mother later for future adverse events that are unlikely to be related to use of the medication.

Menopause

Although menopause was assumed for many years to be associated with an increased incidence of depression, this assumption has not been borne out in empirical studies. Whereas some patients are upset by their loss of fertility, others find menopause liberating (98,99). Patients who have suffered PMS or postpartum depression may, however, be vulnerable to a recurrence of depression at this new time of hormonal change. Patients with depression at the time of menopause should be assessed for psychosocial precipitants and domestic abuse. There are conflicting reports on the effectiveness of hormones for treatment of mood symptoms during menopause (100,101,102,103,104,105). Treatment with SSRIs may ameliorate hot flashes (106).

Depression in elderly patients can cause a pseudodementia, characterized by decreased activity and interest and what appears to be forgetfulness. Unlike patients with organically based dementia, these patients report memory loss rather than trying to compensate and cover up for it. The early stages of dementia also can precipitate depression as patients react to the loss of cognitive abilities.

Approach to the Patient

The severity of depression is determined by the patient's emotional pain and the degree of interference with her normal functioning. Depression is an agonizingly painful and disabling, but readily diagnosable and treatable, disease. Nevertheless, it shares the stigma of all psychiatric disorders. Patients and their families often attribute the signs and symptoms of depression to life circumstances or to a medical condition, either diagnosed or undiagnosed. The persistence of symptoms in the face of a pleasant life situation or the

failure of the patient to respond to attempts at cheering, such as changes of scene, often

exacerbate suffering by provoking guilt in the patient and frustration in her significant others. Patients are more likely to report low energy and general malaise than depressed mood. Physical symptoms are especially common in Asian and some other cultures. Some patients with severe depression continue to function and can appear not only normal but cheerful. The only way to rule out depression is by using the diagnostic criteria (107).

Management

Both antidepressant medication and psychotherapy are effective treatments for depression. There is evidence that a combination of the two produces the best outcomes (108,109,110). Reports about the efficacy of alternative treatments, the most common of which is St. Johns wort, are conflicting (111). Patients should be specifically questioned about their use of herbal and other preparations and encouraged to use those whose components are best standardized. Transcranial magnetic stimulation is a promising research intervention (112,113).

There are many forms of psychotherapy. Those that have been specifically studied for efficacy in the treatment of depression are cognitive-behavioral therapy and interpersonal therapy. These forms of therapy are focused on present thoughts, feelings, relationships, and behaviors. Therapy continues for a set number of sessions, usually no more than 16 weekly sessions, in a prescribed, predetermined progression (114). There is increasing evidence that supportive and psychodynamic psychotherapy may be of help.

It is especially important for the patient to have the opportunity to work out her feelings about having a psychiatric disorder, understand how it has affected her life, and feel comfortable about taking medication or undergoing psychotherapy. Patients often attribute depression to weakness, laziness, or immorality, and they often confuse antidepressants with stimulants, tranquilizers, and other psychoactive drugs. It is useful to provide the patient with written material about depression so that she can review it at her leisure and with her family and friends if they have difficulty understanding her condition.

The types and characteristics of antidepressants are in Table 12.3. **All antidepressants have comparable therapeutic efficacy, and all require up to 2 to 4 weeks to take full effect.** It is not yet possible to identify those patients who will respond best to certain medications, but there is early evidence that depression may be related to specific neurotransmitters and responds differentially to medications affecting a given neurotransmitter. The response to treatment may differ with sex as well, but the data are not sufficient to derive clinical decisions (115).

Table 12.3 Pharmacology of Antidepressant Medications

Drug	Therapeutic Dosage Range (mg/day)	Average (range) of Elimination Half-lives (hours)^a	Potentially Fatal Drug Interactions
Tricyclics			
<i>Amitriptyline (Elavil, Endep)</i>	75–300	24 (16–46)	Antiarrhythmics, MAO inhibitors
<i>Clomipramine (Anafranil)</i>	75–300	24 (20–40)	Antiarrhythmics, MAO inhibitors
<i>Desipramine (Norpramin, Pertofrane)</i>	75–300	18 (12–50)	Antiarrhythmics, MAO inhibitors
<i>Doxepin (Adapin, Sinequan)</i>	75–300	17 (10–47)	Antiarrhythmics, MAO inhibitors
<i>Imipramine (Janimine, Tofranil)</i>	75–300	22 (12–34)	Antiarrhythmics, MAO inhibitors
<i>Nortriptyline (Aventyl, Pamelor)</i>	40–200	26 (18–88)	Antiarrhythmics, MAO inhibitors
<i>Protriptyline (Vivactil)</i>	20–60	76 (54–124)	Antiarrhythmics, MAO inhibitors
<i>Trimipramine (Surmontil)</i>	75–300	12 (8–30)	Antiarrhythmics, MAO inhibitors
Heterocyclics			
<i>Amoxapine (Asendin)</i>	100–600	10 (8–14)	MAO inhibitors
<i>Maprotiline (Ludiomil)</i>	100–225	43 (27–58)	MAO inhibitors
Selective serotonin reuptake inhibitors			
<i>Citalopram (Celexa)</i>	20–40	4–6	MAO inhibitors
<i>Escitalopram (Lexapro)</i>	20–40	5	MAO inhibitors
<i>Fluvoxamine</i>	100–200	2–8	MAO inhibitors
<i>Fluoxetine (Prozac) (now available in a once-a-week preparation)</i>	10–40	168 (72–360) ^b	MAO inhibitors
<i>Paroxetine (Paxil)</i>	20–50	24 (3–65)	MAO inhibitors ^c
<i>Sertraline (Zoloft)</i>	50–150	24 (10–30)	MAO inhibitors ^c
Monoamine oxidase inhibitors (MAO inhibitors)^d			
<i>Isocarboxazid (Marplan)</i>	30–50	Unknown	For all three MAO inhibitors: vasoconstrictors, ^e decongestants, ^e meperidine, and possibly other narcotics
<i>Phenelzine (Nardil)</i>	45–90	2 (1.5–4.0)	
<i>Tranylcypromine (Parnate)</i>	20–60	2 (1.5–3.0)	
5-HT₂ Antagonists			
<i>Trazodone (Desyrel)</i>	150–600	8 (4–14)	
<i>Nefazodone (Serzone)</i>	300–500	3	
Others			
<i>Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL)</i>	225–450	14 (8–24)	MAO inhibitors (possibly)
<i>Mirtazapine (Remeron)</i>	15–45	20–40	
<i>Venlafaxine (Effexor, Effexor-XR)</i>	75–375	5	

<i>Duloxetine (Cymbalta)</i>	20–60 bid	8–17
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^aHalf-lives are affected by age, sex, race, concurrent medications, and length of drug exposure.

^bIncludes both *fluoxetine* and *norfluoxetine*.

^cBy extrapolation from *fluoxetine* data.

^dMAO inhibition lasts longer (7 days) than drug half-life.

^eIncluding *pseudoephedrine*, *phenylephrine*, *phenylpropanolamine*, *epinephrine*, *norepinephrine*, and others.

MAO, monoamine oxidase; bid, two times a day.

Modified From **Depression Guideline Panel**. *Depression in primary care: detection, diagnosis, and treatment*. Quick reference guide for clinicians, no. 5. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1993:15; AHCPR pub. no. 93-0552, with permission.

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It is sensible to use a more activating agent in a lethargic patient and a more sedating agent in an agitated patient. Nonetheless, responses vary on an individual basis, even within the same class of medications. The choice of antidepressant, therefore, is based on side effects, dosage, cost, and the physician's clinical experience (Table 12.4). Patients tend to respond to medications that have worked for them in the past and to those that have worked for depressed family members. It is essential to continue active management not only until the patient has responded but also has returned to her previous level of mood and function through the usual duration of a depressive episode: 9 to 12 months for major depression. If the patient does not recover completely, she should be referred to a psychiatrist (116).

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	<i>Side Effect^a</i>						
	<i>Central Nervous System</i>			<i>Cardiovascular</i>			<i>Weight Gain (more than 6 kg)</i>
	<i>Anticholinergic^b</i>	<i>Drowsiness</i>	<i>Insomnia Agitation</i>	<i>Orthostatic Hypotension</i>	<i>Cardiac Arrhythmia</i>	<i>Gastrointestinal Distress</i>	
<i>Amitriptyline</i>	4+	4+	0	4+	3+	0	4+
<i>Citalopram</i>	0.5	0.5	0.5	0	0	1.5	0
<i>Desipramine</i>	1+	1+	1+	2+	2+	0	1+
<i>Doxepin</i>	3+	4+	0	2+	2+	0	3+
<i>Imipramine</i>	3+	3+	1+	4+	3+	1+	3+
<i>Mirtazapine</i>	0.5–1	4	0.5	0.5	0	0	4

<i>Nortriptyline</i>	1+	1+	0	2+	2+	0	1+
<i>Protriptyline</i>	2+	1+	1+	2+	2+	0	0
<i>Trimipramine</i>	1+	4+	0	2+	2+	0	3+
<i>Venlafaxine</i>	0.5	0.5	2	0	0.5	3	0
<i>Amoxapine</i>	2+	2+	2+	2+	3+	0	1+
<i>Maprotiline</i>	2+	4+	0	0	1+	0	2+
<i>Nefazodone</i>	0.5	0.5	0	2	0.5	2	0.5
<i>Trazodone</i>	0	4+	0	1+	1+	1+	1+
<i>Bupropion</i>	0	0	2+	0	1+	1+	0
<i>Fluoxetine</i>	0	0	2+	0	0	3+	0
<i>Paroxetine</i>	0	0	2+	0	0	3+	0
<i>Sertraline</i>	0	0	2+	0	0	3+	0
Monoamine oxidase inhibitors	1	1+	2+	2+	0	1+	2+

^aNumerals indicate the likelihood of side effect occurring ranging from 0 for absent or rare to 4+ for relatively common.

^bDry mouth, blurred vision, urinary hesitancy, constipation.

From **Depression Guideline Panel**. Depression in primary care: detection, diagnosis, and treatment. Quick reference guide for clinicians, no. 5. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1993:14; AHCPR pub. no. 93-0553, with permission.

Tricyclic Antidepressants

Tricyclic antidepressants are the oldest antidepressants still in use and are available in generic preparations. They all have significant anticholinergic side effects that may be problematic in medically ill and elderly patients. They are associated with some slowing of intracardiac conduction; this side effect can be tolerated and managed in all but a few

patients, and it can be therapeutic for those with hyperconductibility. Tricyclic antidepressants should be taken in divided doses through the day, although bedtime dosing may help patients who have difficulty sleeping. Some tricyclic agents, such as *nortriptyline*, have "therapeutic windows"—blood levels above or below which they are not effective—that must be monitored. The average dose for tricyclic agents is 225 mg/day in divided doses. **The most important drawback of tricyclic medications is their lethality in overdose, which is especially important because they are used with depressed patients who are already at risk for suicide. In the rare event that that they must be used by a potentially suicidal patient, the patient must be given only a few pills at a time.** Some medication plans, private or public, require that treatment begin with the least expensive generic medication, and that the patient fail first before a newer compound will be provided. The

clinician may have to serve as advocate for the patient when this is not a clinically acceptable approach.

Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors are especially effective for atypical depression, which is associated with abnormally increased sleep and appetite. They require dietary restrictions and can be used only in patients who are able to understand and comply with those restrictions to avoid hypertensive crises.

Selective Serotonin Reuptake Inhibitors

SSRIs pose few risks of medical or suicidal complications. Side effects include anxiety, tremor, headache, and gastrointestinal upset (either diarrhea or constipation), and usually abate within a few days of the onset of treatment. **A more serious side effect is loss of libido and interference with orgasm** (117). Patients may be reluctant to report sexual side effects, but they may discontinue treatment because of them. Some women are willing to accept SSRIs as an acceptable price to pay for recovery, especially considering that depression interferes with their sexual functioning. Female patients are frequently concerned about weight gain. In one study, it appeared that a weight gain of 5 to 7 pounds may be attributed to an SSRI; the return of normal appetite may also lead to weight gain. Concerned patients should be advised to watch their diets carefully while taking the medication. There is some evidence that *bupropion* causes less weight gain than SSRIs.

SSRIs are administered in a once-a-day regimen, with little need for dosage adjustments in most cases. It is important to continue treatment until the patient is fully recovered. SSRIs have long half-lives, so occasional missed doses do not constitute a problem. There is an SSRI withdrawal syndrome, generally characterized by flulike symptoms and sleep problems (118). Patients should be cautioned not to discontinue their medications without consulting the physician, and only then by gradually decreasing the dose. As with most medications, antidepressants were not initially tested in older women, but several are under consideration by the U.S. Food and Drug Administration for use in this age group (119).

Atypical Agents

Medications considered atypical include *venlafaxine* (120,121,122), *lithium* salts, and anticonvulsants, which are effective mood stabilizers used for bipolar disorders (123,124). *Bupropion* is another atypical agent used for depression as well as seizure disorders. *Bupropion* is now available in a once-a-day preparation. It lowers the seizure threshold slightly more than other antidepressants and should be avoided or used with caution in patients who have a history of head trauma. It is used, under a separate trade name, for smoking cessation, and thus is particularly useful for smokers who are depressed. *Bupropion*

seems to cause fewer sexual side effects than the SSRIs and may decrease these side effects when added to an SSRI regimen.

Suicide

The most critical issue in the assessment and referral of depressed patients is the possibility of suicide. Following are the risk factors for suicide:

- **Depression**
- **Recent losses**
- **Previous suicide attempts, even if seemingly not serious**
- **Impulsivity**
- **Concurrent alcohol or substance abuse**
- **Current or past physical or sexual abuse**
- **Family history of suicide**
- **A plan to commit suicide**
- **Access to the means to carry out the plan**

Women attempt suicide more frequently than men, but men complete the act more frequently than women (125,126). This is probably because men use more drastic or irreversible means, such as firearms, whereas women tend to overdose and can be treated if discovered. Suicide can occur in the context of severe personality disorder and other conditions as well as a result of depression.

It would seem that someone who had repeatedly made suicidal gestures is more interested in the responses of others than in ending her life. However, **past attempts or gestures increase the risk of completed suicide. Patients who have made a suicide attempt should be queried about the following risk factors: the intent to die (rather than escape, sleep, or make people understand her distress); increasing numbers or doses of drugs taken in**

a progression of attempts; and drug or alcohol misuse, especially if it, too, is increasing. Most people who commit suicide have consulted a nonpsychiatric physician within the prior month.

A possible link between SSRI use and suicidal and homicidal behavior has received a great deal of attention in the press. These reports generally fail to take into account the fact that many individuals who take antidepressants take them because they are suicidal. They also confuse suicidal ideation with suicide attempts and completed suicide.

Inquiry about suicidal ideation and behavior is an inherent part of every mental status examination and is mandatory for every patient with past or current depression or evidence of self-destructive behavior. The inquiry can follow from discussion of difficulties in the patient's life or mood or be introduced with a comment that almost everyone has thoughts of death at one time or another. Nonsuicidal patients will immediately volunteer that they have had such thoughts and that they have no intention of acting on them. They will often add reasons such as they have too much to look forward to, it is against their religion, or it would hurt their family.

It is important to distinguish between the wish to be dead and the intention to kill oneself. A patient in a painful life situation—a chronic, painful, or terminal medical condition, the birth of a severely damaged child, or a grievous loss—may express a wish to die, and even refuse recommended medical care but emphatically and honestly disavow any intention of actively harming herself. It is only necessary to ask the patient.

If the patient has previously engaged impulsively in self-destructive behavior, without a plan or warning, it is wise to consult a psychiatrist. If a patient is actively contemplating suicide, she must see a psychiatrist immediately. Other mental health

professionals may be helpful but are less likely to have dealt extensively with and assumed responsibility for suicidal patients, to be able to determine whether the patient should be hospitalized, and to have admitting privileges. Until she is in the physical presence of a psychiatrist, or in a safe environment such as a hospital emergency room, a suicidal patient should be observed and protected at all times—every second—whether she is in the consulting room or the bathroom. The staff member assigned to remain with her may not leave to make a telephone call, go to the bathroom, or get a cup of coffee. Family members may offer to monitor the patient and can sometimes be effective, but the health care professional is responsible for ensuring that they understand these necessities. **It is better to risk inconvenience and possible embarrassment to both the gynecologist and the patient than to risk a fatal outcome. Once suicide is a possibility, only a psychiatrist can make the decision that a patient is safe.** Psychiatric referral can also be useful in less dramatic cases: when the gynecologist lacks experience or is overloaded with patients, when a first trial of treatment is unsuccessful or there is uncertainty about the diagnosis, when domestic violence or substance abuse may be present, and when the depression is recurrent.

Anxiety Disorders

Diagnosis

Anxiety is a sense of dread without objective cause for fear accompanied by the usual physical concomitants of fear. Although every human being has anxious feelings from time to time, anxiety disorders are diagnosed when anxiety becomes disabling or so painful as to interfere with an individual's quality of life. The anxiety disorders include generalized anxiety disorder, panic disorder, agoraphobia, specific phobias, obsessive-compulsive disorder, and posttraumatic stress disorder (128,129).

Generalized anxiety disorder is a condition in which anxiety pervades every aspect of a patient's life. She suffers from restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbances. Whereas depressed patients fall asleep more or less normally and then awaken earlier than intended, anxious patients have difficulty falling asleep.

Panic disorder is characterized by panic attacks: acute periods, generally lasting about 15 minutes, with intense fear and at least four of the following symptoms:

- **Diaphoresis**
- **Trembling**
- **Shortness of breath**
- **A choking sensation**
- **Chest discomfort**
- **Gastrointestinal distress**
- **Lightheadedness**
- **A sense of unreality**
- **Fear of going crazy or dying**
-

Paresthesias

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Chills or hot flushes

The attacks can recur with or without specific precipitating events (129). The patient is preoccupied with them and makes behavioral changes she hopes will avert future attacks: avoiding specific situations, assuring herself there is an escape route from certain situations, or refusing to be alone.

The symptoms of panic attacks are often confused with the symptoms of cardiac or pulmonary disease. They lead to many fruitless trips to the emergency department and to

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costly, even invasive, medical investigations. A careful history can establish the correct diagnosis in most cases.

Agoraphobia

Agoraphobia is the avoidance of situations in which the patient fears she may be trapped, such as the center of a row in the theater or driving over a bridge. She fears that such a situation will trigger anxiety or a panic attack and therefore tends more and more to stay at home or limit her sphere of activity to a short list of venues. Agoraphobia and panic disorder can occur separately or together.

Specific Phobias

Specific phobias are irrational fears of certain objects or situations, although the patient recognizes that the object or situation poses no real danger. Of particular concern in gynecology are fear of needles and fear of vomiting. Social phobia causes the patient to fear and avoid situations in which the patient anticipates she will be observed by others in a humiliating light. Patients may alter their lives to avoid these anxieties, interfering with their interpersonal relationships and their ability to carry out their responsibilities, or they may manage to carry on despite considerable psychological pain.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is characterized by obsessions: recurrent impulses, images, or thoughts that the patient recognizes as her own, dislikes, and cannot control; or compulsions: intrusive, repetitive behaviors that the patient feels she must perform to prevent some dire consequence. The disorder can be mild or totally crippling; in one half of the cases, it becomes chronic. This disorder is classified as an anxiety disorder because the obsessions are anxiety provoking, and the compulsions are performed to avoid overwhelming anxiety.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is the result of exposure to an event that threatens the life or bodily integrity of the patient or others. At the time of the trauma, the patient experiences horror, terror, or a sense of helplessness. Afterward, the patient may lose conscious memory of all or part of the event, avoid situations reminiscent of it, and become acutely distressed when she cannot avoid them. She feels numb and detached, without a sense of the future. She is hyperarousable and irritable and has difficulty sleeping and concentrating. She re-experiences the event in nightmares, flashbacks, and intrusive thoughts (130).

Epidemiology

Panic disorder without agoraphobia is twice as common in women as it is in men; panic disorder with agoraphobia is 3 times more common in women. Onset is generally in young adulthood, often following a stressful event. The lifetime prevalence is 1.5% to 3.5%; the 1-year prevalence is 1% to 2%. A substantial percentage of patients experience depressive episodes as well. Phobias are somewhat more common in women, depending on the object of the phobia. The 1-year prevalence is 9%, and the lifetime prevalence is 10% to 11%. Obsessive-compulsive disorder is equally common in women and men, with evidence of familial transmission. Prevalence is 2.5% for lifetime and 1.5% to 2.1% for 1 year. Posttraumatic stress disorder has a lifetime prevalence of 1% to 14%; victims of violence (including child abuse and wife battering) and war are at increased risk. Men and women differ in the types of violence to which they tend to be exposed. Rape, for example, poses a similarly high risk of PTSD in both men and women, but women are more often the victims of rape.

Assessment

Given the relationship between anxiety disorders and traumatic experiences, the presence of signs and symptoms of anxiety disorders should trigger inquiries about abuse. It is important to know how long the patient has suffered from the disorder, what previous attempts have been made to diagnose and treat it, and the effect it has had on her psychological development, life choices, lifestyle, and relationships. In some cases, the entire family will have organized their schedules and activities around the patient's symptoms and limitations; they may not volunteer this information.

Management

Treatment should not be limited to antianxiety medications. Managing, even tolerating, patient anxiety is an anxiety-provoking process; anxiety is contagious and raises

the specter of unlimited demands on the gynecologist's time and energy. Prescribing medication is a familiar and comfortable, if not optimal, way to end a medical interview. The overprescription of benzodiazepines has become a cause for medical and media concern. It is useful to defer the administration of anxiolytic medications until the impact of the physician's support and interest can be assessed (131). Treatment should address the effects on the patient's life and family as well as the signs and symptoms of the specific disease (132).

Benzodiazepines are most useful in acute situations. Use can quickly become chronic, with escalating dosages, diminishing therapeutic effects, and increasing demands on the physician. Women taking benzodiazepines may forget to include them in their medical history. When admitted to the hospital, they may suffer unrecognized withdrawal symptoms, complicating their treatment, or may continue to take medications from a personal supply without informing the medical staff. For chronic anxiety and many cases of acute anxiety, there are more effective and safer medications than benzodiazepines.

It is important to ascertain the source of anxiety or obsessive behavior. Many patients and their families are anxious because of misinformation or misunderstanding about a medical problem or treatment. Few patients can absorb all the information about significant gynecologic conditions at a single visit, but most feel that asking questions will burden the physician or make them look stupid. Patients also suffer anxiety when there is disagreement among family members or medical staff about the diagnosis or recommended treatment. Many patients dread certain aspects of care, sometimes on the basis of past experience or outdated information. A simple explanation or alteration in procedure can alleviate the anxiety. For example, a reassuring family member or friend can be allowed to stay with the patient during a diagnostic test, sedation can be administered orally or by inhalation before an intravenous line is inserted, or the patient can be allowed control over her own analgesia.

Behavioral interventions are extremely useful in managing anxiety without problematic side effects. They include hypnosis, desensitization, and relaxation techniques (133,134,135,136,137). Whereas the use of prescribed medications fosters the patient's dependence, these techniques provide her with tools to cope with her own anxiety. Specialists in behavioral medicine, usually psychologists, are expert in these techniques. Interested gynecologists can master some of them as well.

It is easy to be trapped into a cat-and-mouse game with an anxious and needy patient who has an anxiety or personality disorder. Faced with an obsessive or anxious, talkative, and needy patient in the midst of bedside rounds, clinic, or office hours, the clinician can develop a pattern of avoidance, sometimes alternating with overindulgence stemming from feelings of guilt. This kind of behavior results in sporadic, unpredictable reinforcement of the patient's symptoms and demands for attention and is very likely to increase them. Attempting to escape by appearing distracted or harassed, or yielding with despair to the destruction of the day's schedule and the care of other patients simply heightens the patient's anxiety.

It is preferable to develop a prospective approach. Gynecologists tend to underrate the power of their personal interactions with patients and their own ability to structure and limit those interactions appropriately. A patient with a long list of symptoms can be informed at the beginning of the visit how much time is available and asked to focus on her most important problem, with other problems to be discussed at future, scheduled appointments. Instead of scheduling appointments and returning telephone calls grudgingly in response to patient demands, the gynecologist should inform the patient that her condition requires regular (brief) scheduled visits. If she has been contacting the office more often than visits can reasonably be scheduled, she should be asked to call between visits, at prearranged times, to advise the staff of her progress. There are useful self-help groups for patients with various psychiatric conditions and their families. Although groups focused only on victimization can validate patients' experiences and pain and help them build new lives, they also interfere with their motivation to find other ways to identify themselves and obtain gratification.

Medication does have a place in the management of anxiety disorders (138,139,140).

Table 12.5 describes many of these agents. SSRIs are effective for a variety of anxiety disorders, sometimes in different dosage regimens than those used for depression. Benzodiazepines are effective when taken for acute anxiety or during relatively brief, time-limited (several days) stressful situations. The specific agent should be chosen on the basis of onset of action and half-life. The patient must be admonished to avoid concomitant use of alcohol and to exercise extreme care about driving or engaging in other activities requiring attention, concentration, and coordination.

Table 12.5 Compounds Used for Anxiety					
Medication	Trade Name	Rate of Absorption ^a	Half-Life ^b	Active Long-Acting Metabolite	Comments
<i>Benzodiazepines</i>					
Alprazolam	<i>Xanax</i>	Intermediate	Intermediate	No	Metabolism of benzodiazepines is inhibited by cimetidine, disulfiram, isoniazid, and oral contraceptives. Metabolism of benzodiazepines is enhanced by rifampin. Preferred in elderly patients or patients with poor hepatic functions.
Chlordiazepoxide	<i>Librium</i> , others	Intermediate	Intermediate	Yes	
Clonazepam	<i>Klonopin</i>	Long	Long	No	
Clorazepate	<i>Tranxene</i> , others	Short	Short	Yes	
Diazepam	<i>Valium</i> , others	Short	Long	Yes	Half-life increased 3 or 4 times in elderly patients.
Lorazepam	<i>Ativan</i> , others	Intermediate	Intermediate	No	Preferred in elderly patients or patients with poor hepatic function.

Oxazepam	<i>Serax</i>	Long	Intermediate	No	Preferred in elderly patients or patients with poor hepatic function.
Prazepam	<i>Centrax</i>	Long	Short	Yes	
<i>Atypical agent</i>					
Buspirone	<i>BuSpar</i>				Not effective in panic disorder, little sedation, little risk of dependence or tolerance.
<p>^aLong ≥ 2 hours; Intermediate = 1–2 hours; Short ≤ 1 hour.</p> <p>^bLong > 20 hours; Intermediate = 6–20 hours; Short < 6 hours.</p> <p>From Gilman AG, Rall TW, Nies AS, et al. <i>The pharmacological basis of therapeutics</i>. 8th ed. New York, NY: McGraw-Hill, 1990.</p> <p>From Stotland NL. Psychiatric and psychosocial issues in primary care for women. In: Seltzer VL, Pearse WH, eds. <i>Women's primary health care: office practice and procedures</i>. New York, NY: McGraw-Hill, 1995.</p>					

Patients who fail to respond to a trial of office counseling or medication, who are unable to fulfill their responsibilities, who exhaust the patience and resources of significant others, who pose a diagnostic dilemma, who consume inordinate quantities of medical resources, or whose symptoms are becoming increasingly worse should be evaluated by a psychiatrist.

Somatizing Disorders

Definitions

Somatizing disorders are those in which psychological conflicts are expressed in the form of physical symptoms. There is a spectrum of somatizing disorders based on the degree to which the patient is consciously aware of or responsible for the onset of the symptoms. The spectrum ranges from the deliberate malingerer to the so-called hysteric, who is completely unaware of the link between her psyche and her physical symptom (141).

Malingering

Malingering is the deliberate mimicking of signs and symptoms of physical or mental illness to achieve a tangible personal gain, such as exemption from dangerous military duties or exoneration from criminal responsibility. Factitious disorder, or *Munchausen syndrome*, is a poorly understood condition in which the patient actively causes physical damage to herself or feigns somatic symptoms that result in repeated hospital admissions and painful, dangerous, invasive diagnostic and therapeutic procedures. These patients may introduce feces or purulent material into

wounds or intravenous lines, inject themselves with insulin, or produce hemorrhages.

Given enough diagnostic and therapeutic interventions, significant iatrogenic conditions, such as adhesions from surgery or Cushing's syndrome from the administration of steroids, may develop.

These patients are initially engaging but eventually frustrate the medical staff.

Declaring that the patient "only wants attention" is not helpful. Most people want attention, but very few are willing to go to these lengths to get it. Confirming the diagnosis is a delicate process. When staff members become suspicious, they will be tempted to validate their suspicions by spying on the patient or sending her out of her hospital room on a pretext and then searching her belongings. The latter is generally illegal, and either action, followed by a confrontation, will certainly end the therapeutic relationship and provoke the patient to flee rather than addressing the problem. Unfortunately, calls for a psychiatric consultation usually provoke resentment in the patient and family as well. Patients soon reappear in another medical facility. As a result, there are little data about the etiology, incidence, and management of this condition. Often these patients are medically sophisticated because they or their family members have had some kind of medical training as well as knowledge gained during previous hospitalizations. Mothers may enact this disorder through their children by deliberately making them ill, a condition called **Munchausen's by proxy**. Munchausen's by proxy has gained some popular notoriety, and it has resulted in accusations and loss of custody for some mothers whose children had serious, chronic diseases requiring multiple medical interventions. It will be interesting to see how managed care and shared electronic records affect the occurrence of these conditions.

Somatization Disorder

Somatization disorder consists of multiple physical symptoms for which adequate medical bases cannot be established, with these symptoms leading either to numerous medical visits or to impairment in the patient's performance of her responsibilities. Symptoms must begin before age 30 and continue for many years thereafter. The diagnosis requires symptoms of pain related to at least four different anatomic sites or physiologic functions: two gastrointestinal symptoms, one sexual or reproductive symptom, and one pseudoneurologic symptom or deficit other than pain (seizures, paresis). The patient's perception is that she is "sickly." She responds accurately to questions about her past symptoms and treatments but may not volunteer information about them unless she is asked.

Conversion Disorder

Conversion disorder is the condition formerly called hysteria. The patient's loss of a voluntary motor or sensory function cannot be explained by medical illness, is not deliberately produced by the patient, and appears to be related to psychological stress or conflict. The prognosis is directly related to the length of time from onset to diagnosis and

treatment (142,143,144,145).

Other Somatizing Disorders

***Pain disorder* is a conversion condition with pain as the only symptom. *Body dysmorphic disorder* is preoccupation with a trivial or imagined defect in bodily appearance, a preoccupation that is not alleviated by the many medical and surgical treatments that the patient pursues.** The gynecologist should hesitate to refer such a patient to a plastic or cosmetic surgeon, although specialists tend to be familiar with the condition and should hesitate to perform procedures on these patients.

***Hypochondriasis* is not a matter of a particular number or type of symptoms. It is a patient's (nonpsychotic) conviction or fear that she suffers from a serious disease despite evidence and reassurance to the contrary.** When one disease is ruled out, the patient is either convinced that the diagnosis has been overlooked, or switches her concerns to some other disease. This is the condition Woody Allen portrayed in his earlier movies.

Epidemiology

Somatization is believed to be among the most common and most difficult psychological conditions in office practice. It has been estimated that 60% to 80% of the general population experiences one or more somatic symptoms in a given week, providing an ample substrate for the patient preoccupied with her health. Somatization disorder occurs almost exclusively in women; menstrual symptoms may be an early sign. Lifetime prevalence in women is 0.2% to 2.0%. Conversion disorder occurs 2 to 10 times more frequently in women than in men (there is no sex difference in children), and it is more common in rural and disadvantaged populations with little medical sophistication. Conversion disorder may develop into somatization disorder. Reported rates of somatization disorder range from 11 to 300 per 100,000. Pain disorder is extremely common in both sexes. Hypochondriasis is equally distributed between men and women; prevalence in general medical practice is estimated to be 4% to 9%. There are few statistics about body dysmorphic disorder, but it seems to be equally distributed between men and women, with an average age of onset of about 30 years.

Assessment

Most somatizing disorders are chronic. The goal of treatment in primary care is not to eliminate all the somatic symptoms but to help the patient cope with them with as

little effect on her relationships and responsibilities as possible. Because patients often seek care simultaneously or sequentially from several physicians, it is crucial to ask about all past and current diagnostic procedures, diagnoses, treatments, and responses. Patients' level of function over the years is also important; prognosis is inversely related to chronicity. Chronicity should not be an excuse for a failure to treat the patient; the impact on the lives

of patients and their families can be mitigated even if the condition is not entirely eliminated. For these and most other patients, the gynecologist needs to know what the patient believes is wrong with her and what she believes she needs in the way of diagnostic and therapeutic interventions. When what the patient gets is not what she expects or desires, she is unlikely to comply with the recommended course of action, although she may accept it and pretend to be following it so as to avoid criticism from the physician.

Management

The management of somatizing disorders is focused on the avoidance of unnecessary medical interventions, iatrogenic medical or psychological complications, and disability. Unfortunately, it is never possible to definitively rule out all possible medical causes of a symptom. The literature is full of case presentations of patients with multiple sclerosis, brain tumors, and intermittently flaring infections that have been labeled for years as psychosomatic before the condition was diagnosed correctly. Organic pathology can befall patients with somatizing disorders. Patients who have had benign gastrointestinal symptoms for extended periods can get appendicitis.

Patients who have a somatizing disorder often approach each new clinician as the one who, "unlike the incompetent and insensitive physicians (she) has consulted in the past," will finally get to the bottom of her troubles and cure her symptoms.

The gynecologist must not get caught up in these expectations, but rather remind the patient that symptoms that have resisted diagnosis and treatment for many years are likely to be challenging ones. As with anxious patients, it is important to structure the doctor-patient relationship to avoid giving the patient attention inconsistently and only in response to escalating symptoms and demands. It is best to schedule frequent, brief office visits during which the clinician allots a small amount of time to listen to and sympathize with the patient's somatic symptoms and spends the bulk of the time reinforcing the patient's efforts to function despite her symptoms. Family members should be encouraged to facilitate functionality rather than invalidism.

Unmasking patently psychologically based symptoms by tricking the patient (shouting "Fire!" in the vicinity of a "paralyzed" patient), or documenting the patient's behavior when she does not realize she is being observed, is momentarily gratifying for medical staff but humiliating for the patient. It may force her to relinquish a symptom, at least temporarily, but she will seek care elsewhere, exacerbating her dysfunction, distrust, and demands on the health care system.

Patients with conversion, somatization, and hypochondriacal disorders often benefit from prescriptive behavioral regimens aimed at saving face and improving function. It was once believed that a patient relieved of one symptom would soon substitute another, but this assumption has not been confirmed by empirical evidence. The behavioral regimen should consist of health-promoting activities relevant to the target symptoms, planned in a stepwise progression, and recommended with reasonable medical conviction and authority. For example, the patient with psychogenic difficulty swallowing could be advised to drink only clear liquids, at specified intervals, for a specified number of days, and then go on similarly to

full liquids, purees, soft foods, and finally a regular diet. The patient with difficulties in the extremities can undertake an exercise regimen. The patient's preoccupation with her symptoms can be channeled into documentation of her progress in a log that she brings to her medical appointments. The physician is not bound to peruse the entire document at each visit. If it is too long, the patient can be asked to prepare a summary. This process may enlighten both her and the physician to the relationships between her symptoms

and her diet, relationships, or activities. She should be advised not to dwell on her symptoms apart from this important notation.

It is critical to remember that patients with somatic symptoms that are due to depression, posttraumatic stress disorder and other anxiety disorders, and domestic violence frequently seek care from gynecologists. In the case of domestic violence, the gynecologist is often the only human contact the abuser allows the patient outside the domestic situation (146,147,148). These possibilities must be ruled out before care is directed to symptom management.

There is considerable cross-cultural variation in the extent to which feelings and psychological conflicts are somatized. In many Asian cultures, for example, problems with feelings, behaviors, and interpersonal relationships are almost unheard of; these problems are expressed, diagnosed, and treated somatically. Conversely, some very sophisticated and psychologically informed patients in the West may dismiss serious somatic signs and symptoms as indications of psychological conflict.

Referral

Patients with somatizing disorders may resist mental health referral more adamantly than any other single class of patients. Focused as they are on physical symptoms, these patients can regard referral as a message that their symptoms are not being taken seriously and as a sign of contempt and rejection by the gynecologist. It is particularly useful with these patients to emphasize that distinctions between mind and body are artificial. The brain is part of the body. Our language expresses this synthesis; anxiety causes "butterflies in the stomach," aggravation "gives us a headache," and unwelcome news "gives us a heart attack."

The referral should be framed as support for the patient's suffering rather than as a statement that her problems are "all in her head." The mental health professional should be introduced as a member of the medical team. Some medical institutions have dedicated psychiatric consultation, medical psychiatry, or behavioral medicine services offering expertise in the psychological complications of disease and in somatization disorders. Because so-called somatic and psychological symptoms often coexist and interact, the gynecologist should work in collaboration with the mental health professional. Patients should be given a return appointment with the primary physician, or a request for a telephone contact, at the time of the original mental health referral to reassure them that they are not being dismissed and to inform the primary physician of the results of the consultation.

Personality Disorders

Personality disorders are pervasive, lifelong, maladaptive patterns of perception and behavior. Patients with personality disorders do not consider themselves symptomatic, but rather as treated unfairly by circumstances and other people. They view their own behaviors, which can wreak havoc in the health care setting as well as in patients' lives, as normal, expectable, inevitable reactions to these perceived circumstances. To make matters worse, their behaviors tend to provoke in others the very responses that confirm their expectations; for example, a patient who is convinced that people always abandon her clings desperately to others, eventually driving them away.

Personality disorders are organized into clusters in DSM-IV. Patients often manifest characteristics of several disorders within a cluster and between clusters.

Cluster A

- **Paranoid personality disorder**
- **Schizoid personality disorder**
- **Schizotypal personality disorder**

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Cluster B

- **Narcissistic personality disorder**
- **Histrionic personality disorder**
- **Borderline personality disorder**
- **Antisocial personality disorder**

Cluster C

- **Avoidant personality disorder**

- **Dependent personality disorder**
- **Obsessive-compulsive personality disorder**

Individuals with Cluster A disorders are isolated, suspicious, detached, and odd. Narcissistic patients are grandiose, arrogant, envious, and entitled. Histrionic individuals are flamboyant and provocative. Antisocial patients disregard laws and rules of common decency toward others. Borderline personality disorder causes patients to have difficulty controlling their impulses and maintaining stable moods and relationships. They also engage in self-destructive behaviors. They fluctuate between overvaluation and castigation of the same person or direct these feelings alternately between one person and another. When this happens on a gynecology service or in the office, it can precipitate significant tensions among the staff. Recent research reveals that many women who have been abused are diagnosed as borderline when posttraumatic stress disorder more accurately fits their symptoms. **Posttraumatic stress disorder** is a less stigmatizing and more treatable condition than borderline personality disorder.

Epidemiology

Lifetime prevalence of personality disorders as a group is 2.5%. Cluster A disorders are more common in men. Within Cluster B, 75% of cases are women; the prevalence in the general population is 2%. Personality disorders such as narcissistic personality are more common in the clinical population than in the general population. Among cluster C disorders, dependent personality is one of the most frequently diagnosed. Obsessive-compulsive personality is twice as common in men as in women. It is important to distinguish the personality disorder from the symptomatic obsessive-compulsive disorder. There is a strong association between personality disorders and a history of childhood abuse. The possibility of an ongoing abusive situation should be considered as well.

Assessment

The impact of personality disorders ranges widely. At one end of the spectrum, the disorder is an exaggerated personality style. At the other end of the spectrum, the individual suffers terrible emotional pain and is unable to function in work roles or relationships, spending significant periods of time in psychiatric hospitals. She characterizes her symptoms of despair as inevitable responses to abandonment or other mistreatment. As the definition implies, the patient will not seek treatment for the signs and symptoms listed in the diagnostic criteria but instead will have complaints about her treatment by others, their responses to her, and the unfairness and difficulties of life in general. Taking the history, the clinician should frame questions in those same terms: How long have these troubles gone on, and how much

do they interfere with her ability to work and relate to others? Personality disorders do not bring patients to gynecologists' offices directly, but they greatly complicate things once patients arrive there.

Management

It generally requires intense and lengthy psychotherapy to effect significant improvement in patients who have personality disorders. However, there is increasing evidence that expert, targeted therapeutic interventions can be successful and that the long-term prognosis is less dire than previously believed. The challenge in the gynecology setting is to minimize contention and drain on medical staff while maximizing the likelihood of effective diagnosis and treatment of the patient's medical problems. The most helpful

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single step is the identification of the personality disorder. Diagnosis enables the gynecologist to recognize the reasons for a patient's problem behaviors, to avoid becoming entangled in fruitless interactions with the patient, and to set appropriate limits.

There is increasing evidence that psychotropic medications are useful adjuncts in the treatment of personality disorders. Treatment should be provided in consultation with a psychiatrist. The patient's ability to use the medication can be compromised by impulsivity, self-destructive tendencies, and unstable relationships. Low doses of major tranquilizers are sometimes helpful, especially when the patient has brief psychotic episodes. Minor tranquilizers pose significant risk of overdose and physical and psychological habituation. They can be prescribed for temporary stresses, but only in a quantity sufficient for several days and with no refill allowed. At the same time, some patients' anxiety, demands, and power struggles are eased when they are given control over their own use of medication. Such an approach requires enough familiarity with the patient to ensure her safety and should be managed by an expert. Because the patient with a personality disorder attributes her problems to others, her symptoms cannot be adduced as reasons for psychiatric referral, but her suffering can be. If a diagnosis of a personality disorder absolutely must be noted in the patient's chart or on insurance forms, it is essential that she be so informed. It is useful to review the DSM-IV-TR criteria with her so that she understands the basis for the diagnosis. All psychiatric diagnoses, but particularly personality disorders, carry a significant stigma.

Adjustment Disorders

Definitions

Adjustment disorders are temporary, self-limited responses to life stressors that are part of the normative range of human experience (unlike those that precipitate posttraumatic stress disorder). The patient has mood or anxiety symptoms that

are sufficient to lead her to seek medical care but that do not meet criteria of sufficient quantity or quality to qualify for psychiatric diagnosis. The diagnosis requires an identifiable stressor, onset within 3 months after the stress begins, and spontaneous resolution within 6 months after the stressor ends. Obviously the latter cannot be determined until the symptoms resolve—but they do rule out the disorder if the symptoms persist beyond that time (149,150).

Adjustment disorders can be distinguished from normal grieving. Grieving produces symptoms similar to those of depression, although depression is somewhat more likely to cause guilt. Interference with function should not persist beyond several months, but some degree of sadness and preoccupation with the lost loved one often goes on for years. Patients with persistently disabling grief should be referred to a mental health professional.

Epidemiology

Adjustment disorders affect men and women equally. An estimated 5% to 20% of patients undergoing outpatient mental health treatment suffer from adjustment disorders. There is little literature on the subject; one study reported a prevalence of 2.3% among a sample of patients receiving care in a walk-in general health clinic.

Management

Patients with adjustment disorders can be treated effectively with brief counseling in the primary care setting. The counseling can be provided by the gynecologist or by a nurse clinician, social worker, or psychologist, preferably a member of the office or hospital staff who is familiar with the gynecologist and the practice. The medical setting is sometimes the only place where the patient can vent her feelings and think

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through her situation. Counseling is aimed at facilitating the patient's own coping skills and helping her to make autonomous decisions about her situation. The gynecologist should follow the patient's progress and facilitate referral to a psychiatrist if symptoms do not resolve.

Eating Disorders

Definitions

The etiology of eating disorders is neurobiological as well as psychosocial (151). **Preoccupation with thinness, sometimes to the point of pathology, is a major problem for women in North America** (152). Only a small number of women profess to be satisfied with their weights and body shapes. Nearly all admit to current or recent attempts to limit food intake. Physicians often share social prejudices against overweight patients and can easily exacerbate patients' concerns by making chance comments. In some cases, such comments by the physician or others can precipitate, if not cause, an eating disorder.

Anorexia nervosa is characterized by severe restrictions on food intake, often accompanied by excessive physical exercise and the use of diuretics or laxatives. Clinical features include menstrual irregularities or amenorrhea, intense and irrational fear of becoming fat, preoccupation with body weight as an indicator of self-worth, and inability to acknowledge the realities and dangers of the condition. Some patients approach gynecologists for care of infertility (153).

Bulimia is characterized by eating binges followed by self-induced vomiting or purging. Patients' weights may be normal or somewhat higher than normal. Patients have drastically low self-esteem, and the condition frequently coexists with depression (154).

Obesity is an increasingly frequent health problem, and there is little evidence that any nonsurgical approach is effective over time. Sensible eating should be encouraged, and fad or crash diets, which are rampant, are medically and psychologically counterproductive (155).

Epidemiology

More than 90% of cases of anorexia and bulimia occur in female patients. The prevalence is 0.5% to 1.0% in late adolescence and 1% to 3% in early adulthood. There is some evidence of familial transmission.

Assessment

The clinician treating the anorexic patient needs to know how much insight she has into her problem and to assess her mood, relationships, and general level of function. Anorexia poses significant risks of severe metabolic complications and death, often from cardiac consequences of electrolyte abnormalities. Thorough physical and laboratory examination is critical; immediate hospitalization may be necessary.

Management

Patients with anorexia or bulimia should be treated by mental health professionals, preferably those with subspecialization in this area. The conditions are highly refractory to treatment; patients can resort to elaborate subterfuges to conceal their failure to eat and gain weight. Up to 50% of cases will become chronic, and approximately 10% of those will ultimately die of the disease. Antidepressant medication is sometimes helpful. Amenorrheic patients should not be treated with ovulation induction. Evaluation for osteopenia and osteoporosis is necessary.

Psychotic Disorders

Definitions

Psychotic disorders are characterized by major distortions of thinking and behavior. They include schizophrenia, schizophreniform disorders, schizoaffective disorders, delusional disorders, and brief psychotic disorders. General medical and toxic conditions must be ruled out in determining the diagnosis. Distinctions between the disorders are based on symptoms, time course, severity, and associated affective symptoms. **The hallmark of psychosis is the presence of delusions or hallucinations.** Hallucinations are sensory perceptions in the absence of external sensory stimuli. Delusions are bizarre beliefs about the nature of motivation of external events. Because there is no reliable definition of "bizarre," a physician working with a patient from an unfamiliar culture must determine whether a given belief is normal in that culture. Delusions and hallucinations are the positive symptoms of schizophrenia. The negative symptoms include apathy and loss of connection to others and to interests. The negative symptoms may be more disabling than the positive. There is increasing evidence that schizophrenia is associated with cognitive deficits.

Epidemiology

As mentioned previously, schizophrenia occurs in approximately 1% of the population worldwide (156). Onset is in the late teens to mid-30s. Women succumb later in life and have more prominent mood symptoms and a better prognosis than men. The risk is 10 times greater for first-degree biologic relatives and for individuals of low socioeconomic status. It is unclear whether indigent status is a precipitating stress or a result of psychotic illness, but, especially as extremely few individuals have private or public coverage for adequate treatment, most people with schizophrenia are indigent.

Assessment

There is wide variability in the functional impact of psychotic disorders. Patients must not be assumed to be incompetent to make medical decisions or lead independent lives, especially if they comply with treatment. Patients must be asked specifically about their living situations and coping skills. When psychotic women have responsibility for the care of children, their ability to do so should be assessed in consultation with a mental health expert. Motherhood and child custody are exceedingly sensitive matters for these vulnerable patients.

A relentlessly downhill course is not inevitable; remissions and recovery can occur. Therefore, the patient's mental status must be examined carefully. Under the pressures of a busy medical setting, psychotic illnesses can be overlooked, only to erupt in the labor room, operating room, or recovery room. Patients who believe that conspiracies or aliens are responsible for their symptoms can answer yes-or-no medical questions without revealing their delusions. Open-ended questions ("Tell me about your symptoms.") are more useful (157).

Sensationalized media accounts of violent crimes committed by psychotic patients exacerbate public misconceptions about these diseases. Statistically, individuals with psychoses are more

likely to be victims than perpetrators of crime. Untreated patients, especially when under the influence of alcohol or other substances, are at somewhat increased risk of violent behavior; treated patients are no more violent than the public in general.

Management

Psychotic illnesses are nearly always managed by psychiatrists. However, a primary care practitioner can readily assume responsibility, in consultation with a psychiatrist, for a stable patient who complies with treatment. When a patient expresses delusions, the clinician may indicate that he or she does not share them, but should not debate with the

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patient (159,160,161). It is important to concentrate on the patient's strengths. She can easily be humiliated by thoughtless epithets or behaviors that betray the expectation of violence or incompetence. Patients with severe cases must be treated with an integrated system of social services, family support, rehabilitation, general medical care, psychotherapy, and psychopharmacology. In the process of referral to a mental health professional, the primary clinician should be clear, matter-of-fact, open, and confident of the possibility of successful treatment (162).

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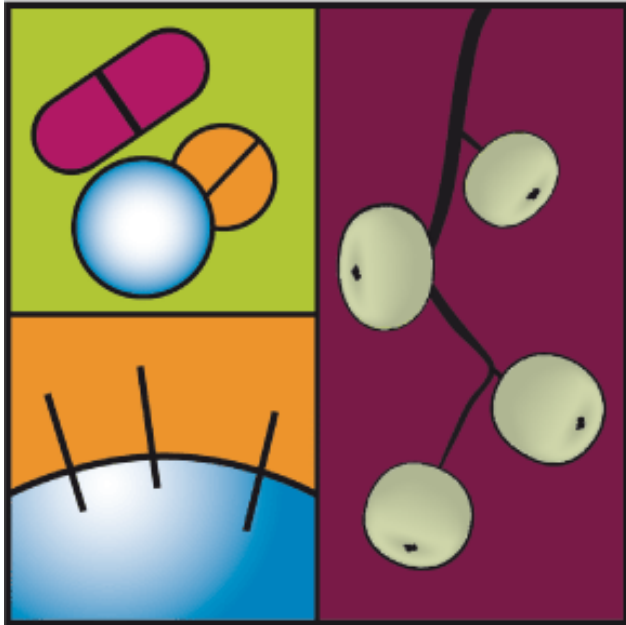
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13

Complementary Therapy

Tracy W. Gaudet



- **The spectrum of complementary and alternative approaches is broad and includes methods worthy of integration into our current practice, as well as ineffective or fraudulent practices that should be avoided.**
-

A complete history should include the patient' s use of complementary and alternative medicine (CAM), particularly botanicals and supplements, as these can have actions ranging from estrogenic to anticoagulant.

- **The U.S. Food and Drug Administration (FDA) does not currently regulate botanicals and supplements, so extra steps must be taken to ensure quality of such products.**
- **The management of many women' s health issues can be enhanced by the integration of selected CAM approaches.**
- **Perceived congruency of values around life and health with CAM providers was predictive of use of these approaches; dissatisfaction with conventional medicine is not a predictor of use of CAM.**
- **Acupuncture has been found to be of benefit in a variety of conditions, including pain, nausea and vomiting of pregnancy, and secondary to chemotherapy.**
- **Mind-body approaches such as stress reduction, visualization, and hypnosis are gaining evidence as valuable adjuncts in a spectrum of women' s health concerns, from surgery to fertility.**

The use of complementary and alternative medicine (CAM) for health maintenance and disease management is on a steady rise in the United States, and for more than 10 years, the number of visits to alternative care providers has exceeded the number of visits to primary care providers. Although evidence exists to support many of these approaches, some approaches are used in the absence of any documented benefit and can potentially be dangerous and even distributed fraudulently (1). The primary users are women, who are frequently making decisions regarding treatment options without the advice of their physicians. Obstetrician–gynecologists are in an excellent position to help guide patients in their treatment choices, counseling them about potentially dangerous alternative treatments and supporting their use of potentially beneficial ones. The most significant challenge is the

lack of training that most obstetrician–gynecologists have in this area; thus, this chapter reviews the domains of CAM as they apply to the practice of gynecology.

Table 13.1 The Five Domains of Complementary and Alternative Medicine

<i>Domains</i>	<i>Examples</i>
Alternative Medical Systems	Homeopathic medicine, naturopathic medicine, traditional Chinese medicine, Ayurveda
Mind-body Interventions	Meditation, prayer, mental healing, creative outlets (art, music, dance)
Biologically Based Therapies	Dietary supplements, herbal products
Manipulative and Body-based Methods	Chiropractic or osteopathic manipulation, massage
Energy Therapies	Biofield therapies, such as qi gong, Reiki, Therapeutic Touch Bioelectromagnetic therapies, such as pulsed fields, magnetic fields, AC or DC fields

National Institutes of Health, National Center for Complementary and Alternative Medicine, <http://nccam.nih.gov/health/whatisacam/>.

Definitions

The concept of complementary and alternative medicine is by definition a relative one. In a landmark publication, the CAM was defined as “medical interventions not taught widely at U.S. medical schools or generally available at U.S. hospitals” (2).

As practices or therapies move in or out of the mainstream in this country, the definition of CAM will change. The spectrum of therapies, practitioners, and products that fall into this category are extremely broad and include everything from botanical medicine to “crystal gazing.” The five domains of CAM are listed in Table 13.1.

The amount of evidence on the use of these approaches varies widely. A significant number of randomized controlled trials, including those with sufficient quantity and quality to allow meta-analyses in some areas, have been done to assess the efficacy of acupuncture, botanical medicine, nutritional approaches, manual therapies, and mind–body medicine. Research in the other domains is much more limited. Many culturally based practices such as shamanism and curanderismo have virtually no research basis. A growing number of randomized controlled

...are being done in spiritual healing and homeopathy, but these techniques remain controversial based on the lack of plausible biophysical mechanisms to justify their efficacy.

Integrative medicine is a distinct entity separate from the practice of CAM.

Integrative medicine neither blindly advocates CAM nor rejects conventional medicine. Integrative medicine is healing oriented and patient centered and adopts a whole-person approach to the treatment of disease and the maintenance of health. It draws on the best practices of medicine, regardless of system of origin. Typically, **integrative medicine would include, in addition to conventional medicine, CAM techniques that may be of benefit, such as nutrition, movement and exercise, mind-body therapy, and spirituality.** Integrative medicine allows the best practices of medicine to be offered to all patients, regardless of their system of origin.

Demographic Data

The first national survey assessing the use of CAM in the United States was done in 1990. This study revealed that 34% of the 1,539 individuals who responded to the survey had used

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CAM in the previous 12 months and that most of these users were women. When extrapolated, these results suggested 425 million visits to alternative care providers occurred that year, which exceeded the number of visits to primary care providers in the same year (388 million visits). An estimated \$13.7 million was spent, \$10.3 million of which was spent out of pocket. This expenditure is comparable to the \$12.8 billion dollars spent out of pocket for all hospitalizations in the United States that same year. Only 28.5% of individuals disclosed this usage to their physician. Of note to conventional health care providers, 71.5% of individuals using these approaches did **not** inform their physicians of their use (2).

This national survey was repeated 7 years later and established the use of CAM in the United States as a significant and growing trend (N = 2,055). When compared with use in 1990, the use of CAM increased from 33.8% to 42.1%. Extrapolations suggest a 47.3% increase in total visits to alternative medicine providers, from 427 million in 1990 to 629 million visits in 1997, again exceeding visits to primary care providers. Not surprisingly, most of these users again were women, with 48.9% of women having used CAM that year, compared with 37.8% of men (1). There was no significant improvement in disclosure, with only 39.8% of users disclosing this information to their physicians. Most users were again found to be paying entirely out of pocket, with no significant change between 1990 (64%) and 1997 (58.3%). Estimated expenditures for alternative medicine services increased 45.2%, and total 1997 out-of-

pocket expenditures related to alternative therapies were conservatively estimated at \$27 billion, which is comparable to the out-of-pocket expenditures for all physician services that year. A study of gynecologic oncology patients revealed that 56% were using CAM, and surveys of menopausal women have showed that 80% were using "nonprescriptive therapies" (3).

The Study of Women's Health Across the Nation (SWAN) found that approximately one half of women were actively using herbal, spiritual, or manipulative therapies (3).

A study examining the use of CAM by women suffering from nausea and vomiting during pregnancy found that 61% reported using CAM therapies, with the most popular being ginger, vitamin B₆, and acupuncture (4). A study evaluating the use of CAM therapies by women with advanced-stage breast cancer revealed that 73% of patients used CAM, with relaxation or meditation techniques and botanicals being used most often (5). The reason most often given for the use of CAM was immune support, followed by the second treatment of cancer. A survey in Washington state exploring use of alternative therapies for menopause revealed that 76% of women were using alternative approaches, with 43% of these women using stress-reduction techniques, 37% using over-the-counter alternative approaches, 32% using chiropractic medicine, 30% massage therapy, 23% dietary soy, 10% acupuncture, 9% naturopathy or homeopathy, and 5% herbalists (6). Of these women, 89% to 100% found these approaches to be somewhat or very helpful. Current users of hormone therapy were 50% more likely to use CAM as those who had never used hormone therapy. **Following the results of the Women's Health Initiative indicating the risks associated with hormone therapy, interest in the use of CAM for management of menopausal symptoms has increased.**

The Attraction

A national survey published in 1998 was the first to explore the very intriguing question of *why* so many patients were turning to CAM (7). Three hypotheses were proposed:

- Dissatisfaction with conventional medicine
- Personal control in their health care
- Philosophical congruence of values around life, health, and wellness

Surprisingly, **dissatisfaction with conventional medicine was *not* predictive of use of CAM. Patients turn to CAM because they are seeking greater congruency of values regarding life, health, and wellness** (7). The message is, then, that people are happy to use conventional medicine when they have a diseased or injured body part, but when their

goal is to improve their health or manage a chronic condition or lifestyle issue, they turn to alternative care providers. Establishing a partnership with patients can help them explore all of the options for maximizing their health.

The reluctance of patients to inform their physicians of their use of CAM creates barriers to the best practice of medicine. Included in the realm of CAM are potentially harmful practices and products as well as potential interactions between effective CAM and conventional approaches. In a 5-year prospective cohort study following women in San Francisco with newly diagnosed breast cancer, 72% were using at least one form of CAM in the management or treatment of their breast cancer. Of these women, 54% disclosed their use to their physician (much higher than the national average), whereas 94% discussed their conventional treatment with their CAM provider (8). Three reasons were given for the patients' lack of disclosure:

- Women anticipated physician disinterest, negative response, or unwillingness or inability to contribute useful information
- Women believed their use of CAM to be irrelevant to their biomedical treatment
- Women did not view disclosure as appropriate coordination of disparate healing strategies

This study highlighted the fact that the use of conventional approaches is well integrated into CAM patient visits, whereas the history of use of CAM is poorly integrated into the conventional medical encounter. Overall, patients' disclosure to their physicians is very cautious, even when the physicians involved would welcome the discussion.

The Challenge

The demographics and trends associated with CAM use create challenges for physicians and dangers for patients. A huge market demand exists, and with it has come an opportunity for products and therapies that may be ineffective, dangerous, or fraudulently marketed. The development of the patient demand has preceded the incorporation of education regarding CAM for medical students, residents, and practicing physicians. As a result, patients make decisions regarding their care without the benefit of medical advice or the coordination of their care by one provider. The best practice of medicine necessitates the integration of all therapies that can benefit the patient and the exclusion of those that can cause harm. Integration of these techniques will require the collaborative, concerted effort of physicians, CAM providers, and patients.

Complementary and Alternative Medicine Techniques

The many types of CAM techniques can be organized by category. Each type is associated with some types of risk or complication. Licensing and certification requirements vary widely from state to state, but most techniques have some type of formal structure for training and accreditation (Table 13.2).

Biologically Based Therapies: Botanical Medicine

Botanical or herbal therapies use botanicals singly or in combination for therapeutic value. A botanical is a plant or plant part that contains chemical substances that act on the body. Botanical or herbal medicines have been studied extensively in Europe, and large multicenter trials are beginning to provide more robust evidence in this country.

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Botanical medicine is the area of CAM most conceptually accessible to patients. Botanicals are the source of the active agents in approximately 25% of prescription drugs and 60% of over-the-counter drugs. In the United States, however, these products are often not perceived as active and are regulated as "dietary supplements," not under the direction of the U.S. Food and Drug Administration (FDA). The most popular botanicals used in the United States are listed in Table 13.3.

Table 13.2 Training and Licensure in Complementary and Alternative Medicine
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<i>Therapy</i>	<i>Training</i>	<i>Licensure</i>
Botanical/herbal medicine	None standardized	Written exam developed by the National Certification Commission for Acupuncture and Oriental Medicine tests for entry-level capabilities in oriental herbal medicine. Passage allows practitioners to call themselves Diplomates of Chinese Herbology (Dipl CH).
Chiropractic	Must complete a 4-year chiropractic college program of study accredited by the Council on Chiropractic Education (CCE)	National
Massage therapy and bodywork	The American Massage Therapy Association (AMTA) accredits 25% of massage training schools. The National Certification Board for Therapeutic Massage and Bodywork (NCBTMB) administers a certification examination used by 24 states. Certification from NCBTMB requires passing this exam and the completion of a minimum of 500 in-class hours of formal education and training.	Offered at the state level in 30 states.
Hypnotherapy		The International Medical and Dental Hypnotherapy Association will certify hypnotherapists if they meet the minimum eligibility requirements and provide referrals.

Clinical hypnosis	Basic certification requires a minimum of 40 hours of ASCH approved workshop training, 20 hours of individualized training, and a minimum of 2 years of independent practice using clinical hypnosis. The advanced level, called approved consultant, requires a minimum of 60 additional hours of ASCH-approved workshop training and 5 years of independent practice using clinical hypnosis.	American Society of Clinical Hypnosis (ASCH) Certification in clinical hypnosis ensures that the certified individual is a bona fide health care professional who is licensed in that state or province to provide medical, dental, or psychotherapeutic services.
Meditation and stress reduction	None	None
Acupuncture	Schools provide 3- or 4-year training programs in oriental medicine that consist of about 2,500 to 3,200 hours.	In most states, the practitioner must provide proof that he/she has attended and graduated from an accredited school or from a school that is in the process of being accredited by the Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM).
		Forty states either license or register acupuncturists as Doctors of Oriental Medicine or Acupuncture Physicians, and about two thirds of these states grant licenses.
	The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) tests entry-level capabilities with a comprehensive written exam, point location exam, and clean needle technique.	An acupuncturist must pass this exam and meet continuing education requirements every 4 years to retain certification and licensure.

Medical doctors can be certified by the American Board of Medical Acupuncture by taking a minimum 300 hours in training.

Naturopathic medicine

Currently only 12 states have licensing laws, and they differ considerably. There are four accredited, 4-year naturopathic medical schools, and a fifth has been granted candidacy status.

Complications and Risks

Botanical medicines are being used by an increasing number of patients, and they often do not advise their clinicians of this use. Certain patients are at risk for drug-botanical interactions or adverse reactions, and patients should be questioned about them (Tables 13.4,13.5). Megadoses of vitamins and supplements also have associated risks and complications, and their use is increasing.

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Because botanicals are regulated as dietary supplements, quality control is challenging. In 1994, the Dietary Supplement Health and Education Act (DSHEA) was enacted. This act makes it legal to refer to the supplement's effect on the body's structure or function or to a person's well-being. Products within the jurisdiction of DSHEA are easily recognized by the following statement on their labels: "This product is not intended to diagnose, treat, cure, or prevent any disease." Because the FDA does not regulate these products, the potential for lack of standardization of products, as well as adulteration or mislabeling, exists.

Pharmacokinetic evaluation also is lacking.

Table 13.3 Top-Selling Herbal Dietary Supplements in the Food, Drug, and Mass Market Retail Channels in 2004 (for 52 Weeks Ending January 2, 2005)

<i>Rank/Herb</i>	<i>Dollar Sales</i>	<i>% Change vs. 1 Year Ago</i>
1. Garlic	\$27,013,420	-11.2
2. Echinacea	\$23,782,640	-14.9
3. Saw palmetto	\$20,334,030	-10.5
4. Ginkgo	\$19,334,010	-12.9
5. Soy	\$17,419,530	-26.6
6. Cranberry	\$13,445,670	+6.8
7. Ginseng	\$12,165,220	-10.2
8. Black cohosh	\$11,984,960	-22.3
9. St. John's wort	\$9,087,829	-12.5
10. Milk thistle	\$7,775,529	+0.8
11. Evening primrose	\$6,088,103	-3.6
12. Valerian	\$3,449,297	-9.2
13. Green tea	\$2,794,783	+22.1
14. Bilberry	\$2,341,301	-17.6
15. Grape seed	\$2,330,281	-11.9
16. Horny goat weed	\$2,203,555	-12.2
17. Yohimbe	\$1,835,313	-21.9
18. Horse chestnut	\$1,564,550	-35.8
19. Eleuthero	\$992,286	-64.4
20. Ginger	\$814,789	-13.8
Multiberbs	\$52,049,290	+29.1
All other herbs	\$11,841,120	-7.5
Total Herb Supplements	\$257,514,900	-7.4

Source: Blumenthal M. Herb sales down 7.4 percent in mainstream market. <http://www.herbalgram.org> 2005; 66: 63.

Botanicals can cause toxicity in one of three ways: (i) the products can be adulterated; (ii) the labels can recommend dosages that exceed appropriate use and cause toxicity even when the product is safe in appropriate dosages; and (iii) Even when they are of good quality and taken in the correct dosage, these products can interact with other supplements and pharmaceutical agents. The Institute of Medicine has recommended the following measures: seed-to-shelf quality control, accuracy

and comprehensiveness in labeling and other disclosure, enforcement against inaccurate and misleading claims, research into consumer use, incentives for privately funded research, and consumer protection against all potential hazards (9).

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Training and Licensure in Biologically Based Therapies

There is no national licensure for botanical or herbal medicine, and there is no national or professional organization that regulates or accredits western and ayurvedic herbal medicine education. However, in 1996, the National Certification Commission for Acupuncture and Oriental Medicine developed a national certification written examination, which tests for entry-level capabilities in oriental herbal medicine. Passage of this examination allows practitioners to call themselves Diplomates of Chinese Herbology (Dipl CH). Currently, there are about 3,200 certified Diplomates in Chinese Herbology nationwide.

Table 13.4 Botanicals: Potential for Interactions with Drugs

<i>Botanical</i>	<i>Drug Class</i>	<i>Type of Interaction</i>	<i>Signs and Symptoms</i>	<i>Type of Evidence</i>
Aloe gel Aloe vera Aloe barbadensis	Diuretics	Potential caused by potassium-depleting effects	Confusion, weakness, irregular heartbeat	Case reports
	Hypoglycemic agents	Potential		Traditional
	All drugs	Reduced effectiveness owing to binding with drug		Traditional
Bilberry Vaccinium myrtillus	Anticoagulants	Potential at high doses	Increased bleeding time	Case reports

Borage	Anticonvulsants	Decreased seizure threshold	Epileptic events	Case reports
Cascara sagrada <i>Rhamnus purshianus</i>	Diuretics	Potentialiation caused by potassium-depleting effects	Confusion, weakness, irregular heartbeat	Case reports
Chamomile, German <i>Matricaria recutita</i>	Sedatives (e.g., chlorpheniramine, trazodone, diazepam)	Potentialiation	Excessive drowsiness, loss of coordination, trouble driving	Theoretical
	Anticoagulants	Potentialiation	Increased bleeding time	Theoretical
Chaparral <i>Larrea tridentata</i>	Phenobarbital	Potentialiation of liver toxicity	Liver toxicity	Theoretical
Chasteberry, chaste tree <i>Vitex agnuscastus</i>	Oral contraceptives and hormone replacement	Reduced effectiveness owing to herb's effect on progesterone		Theoretical
	Anticancer agents for hormone-sensitive cancers	Reduced effectiveness caused by herb's estrogenic activity		Theoretical
Co-enzyme Q10	Anticoagulants	Procoagulant effect	Decreased clotting time	Theoretical
Comfrey <i>Symphytum officinale</i>	Phenobarbital	Potentialiation of liver toxicity	Liver toxicity	Case reports
Danshen <i>Salvia miltiorrhiza</i>	Warfarin	Potentialiation caused by presence of coumarins in herb	Increased bleeding	Case reports
Dong quai <i>Angelica sinensis</i>	Anticoagulants	Potentialiation caused by presence of coumarins in herb	Increased bleeding	Case reports
Echinacea <i>Echinacea purpurea, E. angustifolia, E. pallida</i>	Immunosuppressive agents (e.g., cyclosporin)	Reduced effectiveness	Shivering, fever, muscle weakness	Theoretical

	Drugs metabolized by cytochrome P450 3A4 enzyme (e.g., lovastatin, fexofenadine, triazolam)	Potentialiation caused by inhibition of metabolizing enzyme	Liver dysfunction	In vitro studies
Ephedra Ma huang <i>Ephedra sinica</i>	MAO inhibitors	Potentialiation caused by sympathomimetic action	Excitability, restlessness, hypertension	Case reports
	Caffeine and other stimulants	Potentialiation	Excitability, hypertension, stroke, death	Case reports
	Antihypertensive agents	Reduced effectiveness caused by herb's sympathomimetic actions	Hypertension	Case reports
	Theophylline	Potentialiation caused by sympathomimetic action	Rapid heart rate, anxiety, hypertension	Theoretical
	Cardiac glycosides	Reduced effectiveness	Cardiac arrhythmia	Theoretical
Evening primrose oil (EPO) <i>Oenothera biennis</i>	Phenothiazines, anesthetics, anticonvulsants	Increased risk of seizures as drug and herb lower the seizure threshold level	Epileptic events	Case reports
Feverfew <i>Tanacetum parthenium</i>	Anticoagulants	Potentialiation caused by inhibition of platelet aggregation	Increased bleeding	Case reports
Garlic <i>Allium sativa</i>	Anticoagulants	Potentialiation caused by inhibition of platelet aggregation	Increased bleeding	Case reports
Ginger <i>Zingiber officinalis</i>	Anticoagulants	Potentialiation caused by inhibition of platelet aggregation	Increased bleeding	Case reports
	Antacids	Reduced effectiveness owing to increased gastric secretion	Heartburn	Case reports

Ginkgo <i>Ginkgo biloba</i>	Anticoagulants	Potentialiation caused by inhibition of platelet aggregation factor	Increased bleeding, spontaneous bleeding	Case reports, animal study
	Trazodone	Potentialiation caused by inhibition of drug metabolism	Sedation, coma	Case report
	Thiazide diuretics	Unclear interaction	Hypertension	Case report
Ginseng (Asian) <i>Panax ginseng</i>	Hypoglycemic agents	Potentialiation	Hypoglycemia	Case reports, clinical study
	MAO inhibitors	Potentialiation	Insomnia, headache, tremors	Case reports
	Digoxin	Elevated digoxin levels	Risk of digitalis toxicity, tachycardia	Case reports
	Anticoagulants	Potentialiation caused by inhibition of platelet aggregation and reduced effectiveness reported	Changed bleeding time	Conflicting case reports
	Sildenafil	Potentialiation caused by herb's stimulation of nitric oxide release		Theoretical
	Anti-estrogens	Reduced effectiveness owing to estrogenlike activity of herb		Theoretical
Ginseng (Siberian) <i>Eleutherococcus Senticosus</i>	Digoxin	Elevated digoxin levels, probably caused by interference with digoxin assay	None	Case reports
Guarana <i>Paullinia cupana</i>	Antihypertensives	Reduced effectiveness owing to herb's CNS stimulant effects	Increased blood pressure	Case report
	Halothane	Interaction	Dysrhythmias	Case reports

	Cardiac glycosides	Increased sensitivity to drug caused by increased potassium secretion		Case reports
	Diuretics	Increased sensitivity to drug caused by increased potassium secretion	Diuresis	Case reports
	CNS stimulants	Potential caused by herb's caffeine content (up to 5%)	Restlessness, insomnia, excitability	Theoretical
<i>Kava Piper methysticum</i>	Anxiolytics	Potential	Tremors, somnolence	Case reports
	Alcohol	Potential	Increased impairment, hypnotic effects	Clinical study
	Anticoagulants	Potential	Increased bleeding	Theoretical
	MAO inhibitors	Potential	Hypertension	Theoretical
<i>Kelp, bladderwrack Fucus vesiculosus</i>	Thyroid-hormone replacement therapy	Interference as the herb contains iodine		Theoretical
<i>Licorice Glycyrrhiza glabra</i>	Prednisolone, hydrocortisone	Potential caused by reduced plasma clearance	Hypertension, edema	Case reports, clinical studies
	Thiazide diuretics	Increased risk of hypokalemia caused by increased urinary excretion of potassium		Case reports
	Antihypertensives (e.g., spironolactone)	Reduced effectiveness after 4 weeks of herb owing to inhibition of rennin-angiotensin system	Hypertension	Case reports, in vitro studies
	Cardiac glycosides	Increased sensitivity to drugs after 4 weeks owing to hypokalemic effect of herb	Dysrhythmias, hypertension	Theoretical

Psyllium <i>Plantago ovata</i>	Lithium	Reduced effectiveness caused by interference with lithium ionization		Case reports
Red yeast rice <i>Monascus purpureus</i>	Statin drugs	Potential as both contain the same class of drugs	Liver damage	Theoretical
Saw palmetto <i>Serenoa repens</i>	Hormone replacement therapy and oral contraceptives	Potential caused by herb's steroidal content		Theoretical
	Anticoagulants	Potential	Bleeding risk	Theoretical
Senna <i>Senna alexandrina, Cassia angustifolia</i>	Diuretics	Potential caused by potassium-depleting effects	Confusion, weakness, irregular heartbeat	Case reports
Stinging nettle <i>Urtica dioica</i>	Hypoglycemic agents	Reduced effectiveness	Hyperglycemia	Clinical study
	NSAIDs	Potential		Theoretical
St. John's wort <i>Hypericum perforatum</i>	Other antidepressants	Potential caused by increased serotonin levels	Euphoria, drowsiness, muscle twitching, seeping, diarrhea, loss of consciousness	Case studies
	Various drugs metabolized via cytochrome P450 (e. g., cyclosporin, oral contraceptives, theophylline, HIV protease inhibitors)	Reduced plasma levels of drugs caused by induction of cytochrome P450 metabolizing enzymes	Reduced effectiveness of drugs taken concomitantly	Case reports, clinical studies
	Anticoagulants	Reduced effectiveness	Loss of anticoagulant effect	Case reports
	Digoxin	Reduced effectiveness	Loss of cardioprotective effect	Clinical study
	MAO inhibitors	Potential	Elevated blood pressure	<i>In vitro studies</i>

	Photosensitizing agents (e.g., chlorpromazine, tetracyclines, interferons, isotretinoin)	Potential of photosensitivity	Rash sunburn	Animal studies
Valerian officinalis	Barbiturates and other CNS depressants	Potential	Prolonged sleep and drowsiness, increased risk of falls	Case reports
Yohimbine Pausinystalia Yohimbe, Corynanthe yohimbe	Tricyclic antidepressants	Potential of hypertension by drug	Hypertension, especially in hypertensive patients	Case reports
	Spironolactone	Reduced effectiveness caused by potassium-depleting effects	Hypertension	Theoretical
MAO, monoamine oxidase; CNS, central nervous system; NSAIDs, nonsteroidal anti-inflammatory drugs; HIV, human immunodeficiency virus.				

Manipulative and Body-based Methods

Chiropractic Medicine

Chiropractic medicine focuses on the relationship between structure (primarily the spine) and function, and how that relationship affects the preservation and restoration of health. It uses manipulative therapy as an integral tool. Chiropractors can legally do more than manipulate and align the spine, including taking a medical history, performing a physical examination, and ordering lab tests and x-rays to determine a diagnosis. The spectrum of chiropractors varies in terms of the conditions treated with manipulation. Although

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some practitioners limit their practice primarily to musculoskeletal problems, others claim to offer effective treatment for virtually any medical condition. It should be noted that they are referred to as doctors, which can be misleading to patients.

Table 13.5 Selected Risk Factors for Adverse Reactions or Drug Interactions with Botanicals

- Bleeding disorders or anticoagulated
- Seizure disorders
- Radiation ± chemotherapy
- Immunosuppression
- Diabetes
- Pregnancy
- Renal insufficiency
- Liver disease
- Heart failure
- Electrolyte imbalances
- Patients on sedatives/anxiolytics/CNS depressants/oral contraceptives/diuretics/MAO inhibitors/antiretroviral drugs
- Undiagnosed medical conditions

CNS, central nervous system; MAO, monoamine oxidase.

Complications and Risks

The most significant risk associated with chiropractic medicine is stroke.

Vertebrobasilar accidents occur mainly after a cervical manipulation with a rotatory component. Estimates of vertebrobasilar accidents range from 1 per 20,000 patients to 1 per 1 million cervical manipulations. The average age of patients with vertebrobasilar accidents is 38 years. The second most common complication of spinal manipulation is cauda equina syndrome related to progression of disk herniation. The incidence of cauda equina syndrome is estimated to be less than 1 per 1 million treatments.

Training and Licensure

There is a national process for licensure for chiropractic medicine to which all 50 states adhere. Chiropractors must have completed a 4-year chiropractic college program of study accredited by the Council on Chiropractic Education (CCE).

Massage Therapy and Bodywork

Massage therapy involves manipulation of the soft tissues of the body to normalize those tissues. A wide variety of approaches are available that include deep-tissue massage, Swedish massage, reflexology, rolfing, and many others. A number of randomized controlled trials have documented the value of massage therapy, particularly in pediatric conditions such as childhood asthma.

Massage therapy and bodywork are used by a wide array of people seeking the benefits of massage, which include physical relaxation, reduced anxiety, increased circulation, and pain relief. Specific indications for massage include treatment of acute low-back pain and lymphatic massage for patients with lymphedema from conditions such as postmastectomy extremity edema. Massage is used by various practitioners, including physicians, physical therapists, osteopathic physicians, chiropractors, acupuncturists, nurses, and massage therapists.

Complications and Risks

Massage should not be used in the presence of bleeding disorders, phlebitis and thrombophlebitis, edema that is due to heart or kidney failure, fever or infections that can be spread by blood or lymph circulation, and leukemia or lymphoma.

Massage should not be performed on or near malignant tumors and bone metastases; over bruises, unhealed scars, or open wounds; on or near recent fracture sites; or over joints or other tissues that are acutely inflamed.

Training and Licensure

There is no national licensure in massage therapy, but licensure is offered in 30 states. One fourth of the massage training schools are accredited by the American Massage Therapy Association (AMTA). The National Certification Board for Therapeutic Massage and Bodywork (NCBTMB) administers a certification examination, and 24 states use it for licensure. The NCBTMB is an independent, private, nonprofit organization, founded in 1992, that fosters high standards for therapeutic massage and bodywork professionals. Currently, there are more than 40,000 nationally certified massage therapists and body workers in the United States. Certification by NCBTMB requires successful completion of the examination as well as the completion of a minimum of 500 in-class hours of formal education and training.

Mind-body Interventions

Clinical Hypnosis and Imagery

Hypnosis involves the induction of trance states and the use of therapeutic suggestions. Hypnosis has documented value for a variety of psychological conditions as well as pain control and recovery from surgery.

Complications and Risks

Hypnotized persons occasionally report unanticipated negative effects during and after hypnosis. The spectrum of reported effects has encompassed minor transient symptoms such as headaches, dizziness, or nausea in experimental situations to less frequent symptoms of anxiety or panic, unexpected reactions to an inadvertently given suggestion, and difficulties in awakening from hypnosis. More serious reactions following hypnosis have generally been attributed to the misapplication of hypnotic techniques, failure to prepare the participant, and preexisting psychopathology or personality factors. There have been no known deaths attributed to the use of hypnosis.

False memories of suggested events that did not occur in reality, particularly when legal and interpersonal battles are involved, can be viewed as an untoward reaction to psychotherapeutic procedures. In hypnotic as well as nonhypnotic situations, leading and suggestive overtures can produce false memories. Because hypnosis involves direct and indirect suggestions, some of which may be leading in nature, and because hypnosis can increase confidence of recalled events with little or no change in the level of accuracy, therapists must be vigilant to the problem of creating false memories.

Training and Licensure

There is no national or state licensure for hypnotherapists. The International Medical and Dental Hypnotherapy Association will certify hypnotherapists if they meet the minimum eligibility requirements and will provide referrals.

American Society of Clinical Hypnosis (ASCH) certification in clinical hypnosis is distinct from other certification programs in that it ensures that the certified individual is a health care professional who is licensed in his or her state or province to provide medical, dental, or psychotherapeutic services. Certification by ASCH distinguishes the professional practitioner

from the lay hypnotist. There are two levels of certification, each of which is simply called *certification*, and requires, among other things, a minimum of 40 hours of ASCH-approved workshop training, 20 hours of individualized training, and a minimum of 2 years of independent practice using clinical hypnosis. An advanced level, called *approved consultant*, recognizes individuals who have obtained advanced training in clinical hypnosis and who have extensive experience in using hypnosis within their professional practices. Certification at this level requires a minimum of 60 additional hours of ASCH-approved workshop training and 5 years of independent practice using clinical hypnosis.

Meditation and Stress Reduction

Meditation is a self-directed practice for relaxing the body and calming the mind.

Most meditative techniques have come to the West from religious practices in the East, particularly India, China, and Japan, but it can be found in all cultures of the world. A National Institutes of Health Consensus Panel in 1996 concluded that **mind-body and behavioral techniques were effective in the treatment of stress-related conditions and insomnia**. *Mindfulness-based stress reduction (MBSR)*, based on *Vipassana meditation* from India, has been promoted in this country. This technique is based on the cultivation of mindfulness, an intentional, focused awareness of nonjudgmental attentiveness to experiences in the present moment. Vipassana meditation, one of India's most ancient techniques of meditation, was taught more than 2,500 years ago as a remedy for universal ills.

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Transcendental meditation (TM) is a simple, natural, effortless procedure practiced for 15 to 20 minutes in the morning and evening while sitting comfortably with the eyes closed. During this technique, the individual experiences a unique state of restful alertness.

Transcendental meditation has been shown to be useful in the treatment of hypertension.

The relaxation response is a physical state of deep rest that changes the physical and emotional responses to stress (e.g., decrease in heart rate, blood pressure, and muscle tension). If practiced regularly, it can have lasting effects when encountering stress throughout the day.

Complications and Risks

Meditation rarely may lead to a "spiritual emergency," defined as a crisis during which the process of growth and change becomes chaotic and overwhelming as individuals enter new realms

of spiritual experience. It is included in the DSM-IV diagnostic category "religious or spiritual problem." Types of spiritual emergency include but are not limited to various categories: loss or change of faith, existential or spiritual crisis, experience of unitive consciousness or altered states, psychic openings, possession, near-death experience, kundalini, shamanic journey, or difficulties with a meditation practice.

Training and Licensure in Meditation and Stress Reduction

There is no nationally recognized licensing or certification procedure for teachers of meditation.

Energy Therapies

Energy therapies involve the use of energy fields. They are of two categories:

- *Biofield therapies* are intended to affect energy fields that purportedly surround and penetrate the human body. Some forms of energy therapy attempt to manipulate biofields by applying pressure or manipulating the body by placing the hands in, or through, these fields. Examples include qi gong, Reiki, and therapeutic touch.
- *Bioelectromagnetic-based therapies* involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating current or direct current fields.

Complications and Risks

Energy-based therapies are the least well researched and the most diverse of all CAM modalities. It is, therefore, not possible to address potential complications and risks.

Training and Licensure in Energy-based Therapies

Given the wide array of therapies that fall under this category, the levels of training vary tremendously from modality to modality.

Alternative Medical Systems

Oriental Medicine and Acupuncture

Acupuncture is a therapeutic intervention that is used in many Asian systems of medicine. It is based on the theory that there are energy channels called meridians that run throughout the body and that disease results from blockages of this energy. Acupuncture

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is used as one approach to release these blockages. It involves stimulating specific anatomic points in the body along these meridians by puncturing the skin with a very fine needle (32 gauge or smaller). There are many distinct styles of acupuncture, which include traditional oriental medicine, Japanese manaka style, Korean hand acupuncture, and the Worsley five-element method.

Given the western, biomedical model, acupuncture is difficult to comprehend. There is, however, an intriguing and growing body of research on this technique. In one study involving stimulation of an acupuncture point that corresponds to the visual cortex and is located on the lateral aspect of the foot, magnetic resonance imaging detected activity of the visual cortex of the brain equivalent to the activity seen when a light is shone in the eye. No activity was seen when an acupuncture needle was placed one centimeter away from the designated acupuncture point (10). Many of the CAM approaches that claim to have an effect and yet seem to be inconsistent with the biomedical model may deserve further investigation.

A 1997 National Institutes of Health Consensus Panel established that there was convincing evidence for the use of acupuncture in the treatment of postoperative dental pain as well as nausea and vomiting. Other indications that were considered promising and worthy of more research included headache, low-back pain, stroke, addiction, asthma, premenstrual syndrome, osteoarthritis, carpal tunnel syndrome, and tennis elbow. There is an extensive body of animal research supporting the neurophysiologic effects of acupuncture on the endorphin system.

Complications and Risks

Bruising and minor bleeding is the most common complication of acupuncture and occurs in about 2% of all needles placed. It rarely requires treatment other than local pressure to the needle site. The most significant risk of acupuncture is infection, and 126 cases of hepatitis have been documented. The only reported cases of infection from acupuncture occurred in instances in which needles were reused. The risk of transmissible infection is eliminated by one-

time use of disposable needles, which is now standard practice in the United States. Pneumothorax is the second most significant risk of acupuncture with 66 reported cases. The needles are 32 gauge or smaller; therefore, a chest tube usually is not required for treatment. Five deaths related to acupuncture have been reported. Two deaths were caused by staphylococcal septicemia, two resulted from pericardial tamponade, and one patient died during treatment for acute asthma.

Training and Licensure

Currently there is no national licensure for acupuncture. Educational requirements for state licensure for acupuncture vary. Forty states either license or register acupuncturists as *doctors of oriental medicine* or *acupuncture physicians*. About two thirds of these states grant licenses. To get licensed in most states, the practitioner must provide proof that he or she has attended and graduated from an accredited school or from a school that is in the process of being accredited by the Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM). These schools provide 3- or 4-year training programs in oriental medicine that consist of about 2,500 to 3,200 hours.

The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) administers a standardized examination to test entry-level capabilities in acupuncture that consists of a comprehensive written examination, point location examination, and demonstration of clean needle technique. An acupuncturist must pass this examination and meet continuing education requirements every 4 years to retain certification and licensure. In the United States, there are about 17,000 practitioners currently

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certified in acupuncture by the NCCAOM, and many states have adopted this examination as the basis for licensure.

Medical doctors can practice acupuncture, though physician acupuncture practitioners are seldom as fully trained in the art as nonphysician licensed acupuncturists. To be certified by the American Board of Medical Acupuncture, physicians must take a minimum 300 hours in training.

Homeopathy

Homeopathic medicine is a CAM alternative medical system based on the work of the German physician and chemist Samuel Hahnemann approximately 200 years ago. **In**

homeopathic medicine, there is a belief in “the law of infinitesimals” and that “like cures like.” Thus, small, highly diluted quantities of medicinal substances are given to cure symptoms when the same substances given at higher or more concentrated doses would actually cause those symptoms.

Naturopathic Medicine

Unlike oriental medicine or homeopathy, naturopathy does not have a long history of traditional use, nor is it based in a comprehensive system. **Naturopathy views disease as a manifestation of alterations in the processes by which the body naturally heals itself and emphasizes health restoration rather than disease treatment.** Naturopathic physicians employ an array of healing practices, including diet and clinical nutrition; homeopathy; acupuncture; herbal medicine; hydrotherapy (the use of water in a range of temperatures and methods of applications); spinal and soft-tissue manipulation; physical therapies involving electric currents, ultrasonography, and light therapy; therapeutic counseling; and pharmacology.

Training and Licensure

There is no national licensure for naturopathy, and licensure at the state level is inconsistent. Currently only 16 states have licensing laws, and they differ considerably. Four 4-year naturopathic medical schools are accredited by the Council on Naturopathic Medical Education.

Patient Care Issues

The Placebo Effect

Only with more rigorous scientific research will the role of the placebo effect in various CAM approaches be further elucidated. Just as with conventional medicine, the effects of certain approaches are more likely than others to be associated with a placebo response. After exposure to a stimulus believed by both the patient and the practitioner to be an active intervention, the body responds physiologically in an equivalent manner. **Approximately one third of patients in placebo-controlled trials of conventional methods experience a placebo response.** It would be of great value to medicine if the placebo response were better understood and could be activated more reliably in patients. There is, however, no evidence that the placebo response is more active in CAM than in conventional approaches.

Quality Control

Quality control issues in CAM are very challenging for several reasons. First, the market demand is huge and is far ahead of the health care system's ability to address issues of regulation, education, or research. Because CAM, by definition, is inclusive of everything that conventional medicine is not, issues of quality control are extremely difficult. The Federation of State Medical Boards has recently developed "Model Guidelines for the Use

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of Complementary and Alternative Therapies in Medical Practice," which were approved by the House Delegates of the Federation of State Medical Boards of the United States, Inc., as policy in April 2002. The intention of this initiative was to provide guidelines that are clinically responsible, ethically appropriate, and consistent with what state medical boards generally consider to be within the boundaries of professional practice and accepted standard of care.

Potential Misuse

In addition to physical risks, patients and physicians alike should be aware of other areas of potential misuse. Two areas are of particular concern. First, given that the dollars being spent out of pocket are so significant, there are some products and some providers whose primary motivation is monetary. Patients can spend significant dollars based on false promises or claims. Second, patients can postpone effective therapy or treatment by turning to CAM modalities exclusive of conventional approaches. This time can be significant in the treatment of many patients' diseases. Factors that should increase suspicion for potential misuse are listed in Table 13.6.

The Potential Benefits: Therapeutic Opportunities

Given all of the risks and uncertainties, it is appropriate to ask the question: Why should physicians educate themselves regarding CAM? The most basic answer is commitment to the best practice of medicine. If patients are using therapies that are potentially dangerous in their action or in their interaction, physicians should be aware of this possibility and counsel them accordingly. Physicians also have a commitment to offer their patients the best treatment options, regardless of their system of origin. If there are CAM therapies that can benefit patients, they should be informed of them.

In addition to this most fundamental of reasons, there are additional therapeutic opportunities offered by CAM, as shown by the following examples:

- Decreased harm of interventions: Chiropractic medicine to treat acute low-back pain and potentially avoid surgery; mind–body approaches to decrease anxiety and need for medical management
- Treatment of conditions when conventional approaches fail: Treatment of nausea and vomiting of pregnancy with acupuncture, vitamin B₆, and ginger
- Prevention: Increased intake of isoflavones to potentially decrease the risk of breast cancer
- Improved outcomes: Successful management of menopausal symptoms in patients at risk for breast cancer

Table 13.6 Factors that Should Increase Suspicion for Potential Misuse

1. Providers or products that make claims that are grandiose and dubious, for example:

- Chiropractors who claim to cure insulin-dependent diabetes or offer alternative approaches to cure cancer
- Providers or products who foster dependence
- Therapists who recommend multiple visits per week or frequent visits for an unlimited period

2. Providers who recommend products that they sell and from which they profit

3. Providers or products that support the use of alternative approaches exclusive of conventional medicine or conventional providers

Doctor–Patient Interaction

One of the greatest barriers regarding issues of CAM is a lack of communication. As multiple studies have shown, most patients do not tell their physicians of their use of CAM. Often, this is the case even when the physicians are receptive to the topic. Given the prevalence of use and the potential for interactions with conventional approaches, it is imperative that questions regarding CAM be integrated into the patient history. Many patients simply do not think of sharing this information with their physicians, so direct and specific inquiry is necessary. Many practices incorporate this information in a separate sheet for patients to fill out and for physicians to review and add to the chart. It is useful to know all CAM therapies that patients have used in the past or are using presently, particularly anything ingestible. If a patient is seeing a CAM practitioner, it is best to specifically ask if they have recommended any supplements or botanicals. Oriental medicine practitioners or acupuncturists, for example, often treat with botanical products or herbal teas. Naturopaths and chiropractors often recommend vitamins and supplements. When patients are asked this history directly in an atmosphere of respect, they usually are very forthcoming, and the most significant barrier has been broken.

Three factors contribute to an interesting dynamic that often arises when discussing issues of CAM with patients. This is an area in which (i) very few physicians have received any formal training, (ii) there is little (albeit increasing) research in the mainstream medical journals, and (iii) there is a tremendous amount of information, of variable quality, in the lay press. All of these factors contribute to a circumstance that often is uncomfortable for physicians. This discomfort is important to recognize because it can contribute to avoidance of the topic altogether. The development of CAM therapies and their integration into the treatment plans is a new and evolving area. It is appropriate to begin the conversation with a patient by explaining that this is new territory in conventional medicine and that you are not an expert. Most patients have already assumed this to be the case, appreciate the honesty, and value the opportunity to discuss these dilemmas. This is a significant step in building a trusting and therapeutic relationship with patients interested in CAM.

It is useful to share the following decision tree with patients when making decisions regarding the use of CAM (Fig. 13.1).

Step One: Assess Potential Harm

Although research regarding CAM approaches is often less than optimal, the potential for any therapy to do harm should be thoroughly evaluated (to the best of available knowledge). It

is necessary to evaluate the potential to cause both direct harm and indirect harm.

Potential for Direct Harm

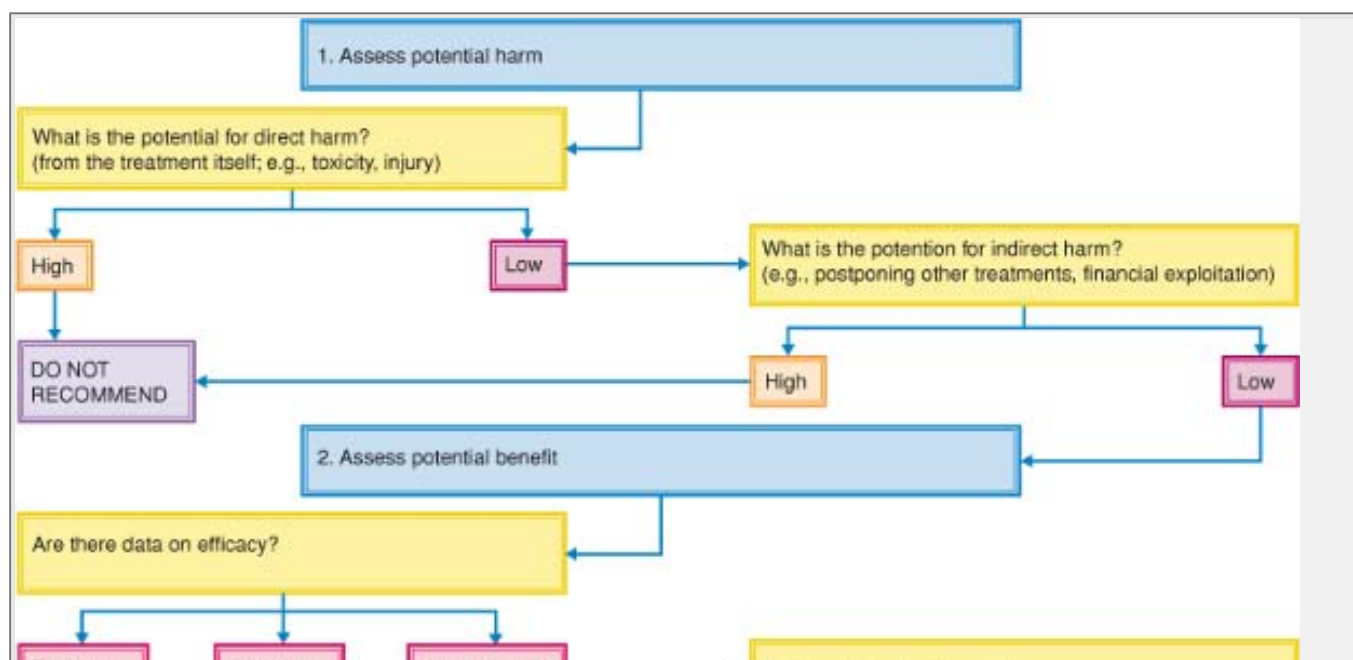
This should include any evidence regarding potential harm directly from the therapy or potential interactions. When lacking good evidence, assessment of the invasiveness of the therapy is a strong predictor of risk.

Potential for Indirect Harm

This should include an assessment of potential harm caused by postponing effective treatments, as well as by financial exploitation. Many CAM approaches are costly, and the patient usually assumes all of the cost. Marketing can prey on vulnerable patients and result in significant and unnecessary expenditures.

Step Two: Assess Potential Benefits

The potential for any approach to be of benefit should be assessed on several levels.



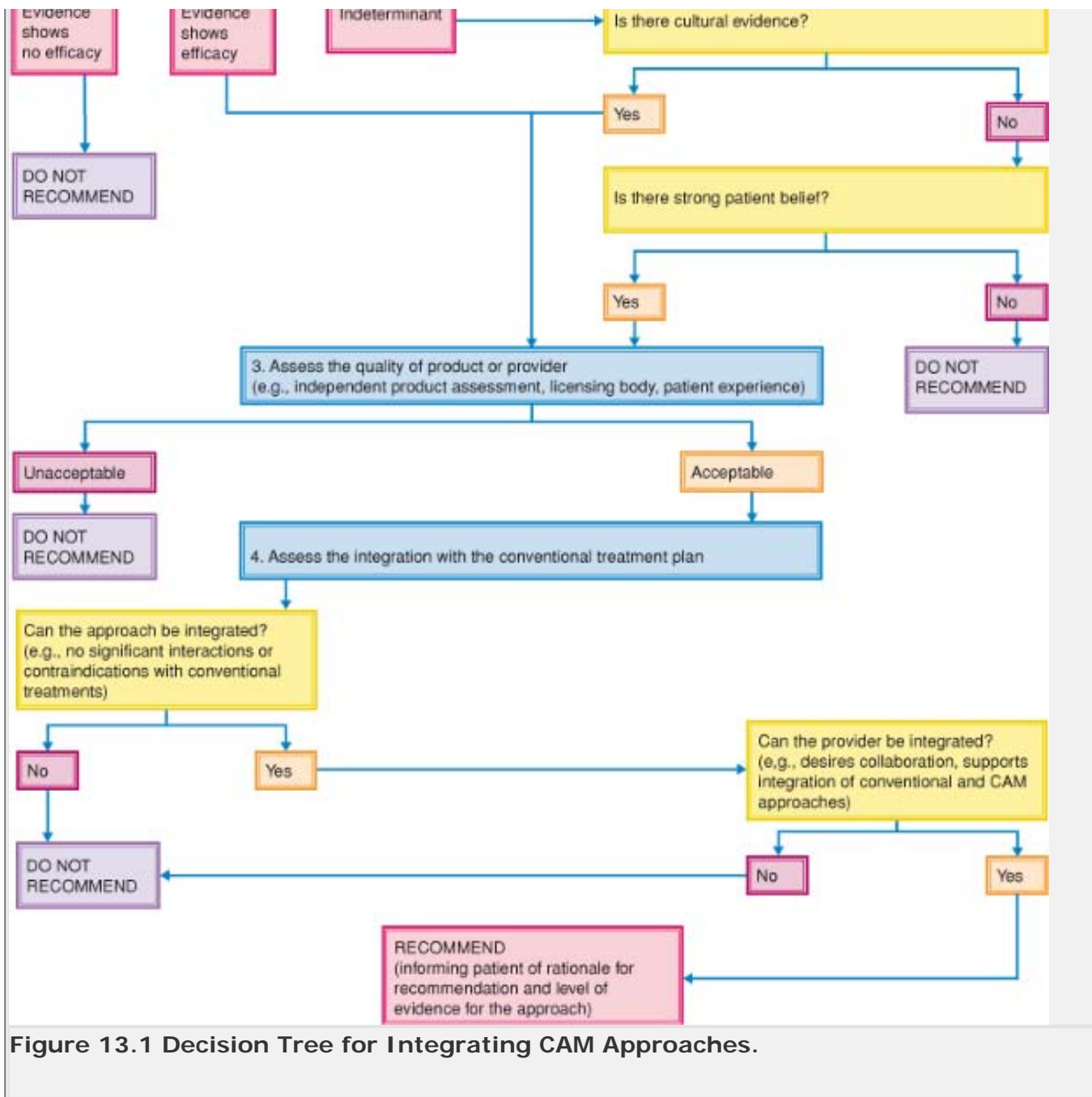


Figure 13.1 Decision Tree for Integrating CAM Approaches.

Scientific Evidence

A review of the peer-reviewed literature should certainly be conducted for evidence of the effectiveness of the approach under consideration.

Cultural Evidence

Another form of useful information is the historic or cultural use of the approach. For example, it is valuable to consider whether a therapy has a long history of use within a given culture. If, on the other hand, the approach has no historic use, this too is important to recognize.

Examples include the use of black cohosh for menopausal symptoms, which has been used for centuries with reported safety and effectiveness, compared with red clover, which has no historic use or track record. Another example would be acupuncture, with thousands of years of use, compared with chelation, which has been in use for a relatively short time and is associated with considerable debate regarding its benefit.

Personal Belief

Another part of the assessment of benefit is to recognize the patient's belief system as it pertains to the approach. If the patient has a strong belief in the approach, and there is no evidence of potential harm, it is often reasonable to support its use. Activating a healing response or a placebo effect can often be very therapeutic.

Step Three: Assess the "Delivery System"

When assessing the delivery system, both products and providers must be considered.

Product

Assessing the history of the manufacturing company and understanding its process of quality assurance can be useful. Referral to independent sources for determining the quality of product and accuracy of labeling also may be useful.

Provider

It can be difficult to assess the skill level of CAM providers. Inquiring about the education of a given provider as well as his or her licensing status (if there is a licensing body for the field) is an important place to start. It also is useful to talk to other patients who have used these

services. Finally, one's own sense of a provider is extremely important.

Step Four: Assess the Integration

Although the individual CAM therapy may have no evidence of harm and be of potential benefit, the way in which it is integrated into the patient's overall treatment plan is important. The same is true for CAM providers.

Approaches

The therapy or approach should be integrated into the overall treatment plan. For example, large doses of antioxidant vitamins should not be used in patients undergoing radiation therapy, as they may counteract the action of the radiation. Likewise, patients with Down's syndrome should not undergo chiropractic manipulation.

Providers

Perhaps most importantly, the potential for integration of the providers is essential to assess. If the intention is to offer the patient the best possible care, all providers, conventional and CAM alike, should be assessed for their willingness to integrate their care for the benefit of their patients. If any providers are unsupportive of conventional medicine, it is critical to recognize this and look for a provider who supports integration of care.

It is useful for each physician to recognize his or her own biases about CAM and willingness to learn about the techniques. At a minimum, physicians should know the basics about which CAM approaches may be of benefit to patients and which may be of harm. Familiarity with resources in the community that are more focused on these areas can serve physician and patient alike.

Specific Gynecologic Issues

Menstrual Disorders

Biologically Based Therapies: Supplements and Botanicals

Premenstrual Symptoms

In a review of randomized controlled trials of CAM approaches in reproductive-age women, the authors concluded that data clearly supported the use of calcium for premenstrual syndrome (PMS) and that initial studies were promising for magnesium, Vitamin B₆, and chasteberry, as well as fish-oil supplementation for dysmenorrhea (11).

Calcium

Multiple studies have shown that calcium, 900 to 1,200 mg/day in divided doses, has at least some effect on symptoms of PMS and premenstrual dysphoric disorder (PMDD), including negative mood, water retention, and food cravings (12). One of the largest studies to date examined the effect of 1,200 mg of calcium per day and reported a 48% decrease in PMS symptoms. In this study, the placebo group also had a 30% reduction in symptoms (12). Although the difference between the groups was statistically significant, it is interesting to note that there tends to be a large placebo effect in these studies.

Magnesium

As a sole agent, there is less evidence on magnesium than calcium, although low magnesium levels have been reported in women suffering from PMS. However, several studies show a significant decrease in PMS symptoms with magnesium supplementation (13,14). Magnesium can be taken 200 to 400 mg/day, in divided doses, either cyclically during the luteal phase or continuously. It also helps to counteract the constipating effects of calcium supplementation.

Vitamin B₆

Vitamin B₆ binds to estrogen and progesterone receptors and has been the subject of most of the randomized controlled trials regarding CAM and PMS. Most controlled studies on vitamin B₆ in the treatment of PMS have limited numbers of patients; therefore, the evidence of positive effects is fairly weak (15). This is a benign therapy in doses of 100 mg or less, however. A systematic review of nine trials indicated significant benefit over placebo for the symptoms of mastalgia, swollen breasts, pain, and depression (16). A recent review of these trials has

shown that most of them have shown some benefit (11). It is important to note that peripheral neuropathies can occur with doses of 200 mg/day or higher and that vitamin B₆ may interact with other medications, specifically those used to treat Parkinson's disease. The recommended starting dose is 50 mg/day with meals, daily.

Vitamin E

Studies performed in the 1940s suggested that vitamin E might be effective in the treatment of menstrual disorders such as PMS. Recent studies have failed to reproduce these results. One study that evaluated vitamin E (in d-alpha tocopherol form) for the treatment of PMS symptoms showed an improvement over placebo (17).

Omega-3 Fatty Acids

There are two major types of omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids act as anti-inflammatory agents in that they shift arachidonic acid metabolism away from PgF_{2a} and increase levels of the less inflammatory PgE₁. Omega-3 fatty acids are essential foods, and levels are extremely low in the average diet of individuals in the United States. They can be increased through dietary means as well as supplements (Table 13.7). One study looked at EFA and PMS and showed no effect. There are, however, some positive studies looking at the effectiveness of omega-3 fatty acids in treating mild depression with fish oils. This

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may be a reasonable approach to try if one of the patient's primary symptoms is mood depression (3 grams, divided with meals) (18). Side effects are rare, but occasionally patients will experience nausea, diarrhea, belching, or an unpleasant taste in the mouth. Omega-3 fatty acids have an anticoagulant effect and are relatively high in calories.

Table 13.7 Omega-3 Content of Foods^a

<i>Fish (3.5 ounce portion)</i>	<i>EPA (mg)</i>	<i>DHA (mg)</i>	<i>Total EPA +DHA (g)</i>	<i>Total Fat (g)</i>
Bass (striped)	184	637	0.8	2.5
Catfish—wild	85	116	0.2	2.4
Catfish—farmed	42	109	0.2	6.8
Clams (about 9 small)	117	124	0.2	1.1
Cod—Pacific	88	147	0.2	0.1
Cod—Atlantic	3	131	0.1	0.8
Crab—Alaska king (about 2/3 leg)	251	100	0.4	1.3
Crab—Dungeness (about ¾ crab)	239	96	0.3	1.1
Fish sticks (about 3)	72	108	0.2	10.2
Flounder and sole	207	219	0.4	1.3
Haddock	65	138	0.2	0.8
Halibut	77	318	0.4	2.5
Herring—kippered	825	1003	1.8	10.5
Herring—pickled	711	464	1.2	15.3
Lobster (Northern)	45	26	0.1	0.5
Mackerel—Pacific and Jack	855	1016	1.6	8.6
Mackerel—Atlantic	428	594	1.0	15.1
Mackerel—King	148	193	0.3	2.2
Mahi mahi (dolphin fish)	22	96	0.1	0.8
Oysters—Pacific, raw (about 1.5)	312	212	0.6	2.0
Oysters—Eastern, wild, raw (about 6)	228	248	0.5	2.1
Oysters—Eastern, wild (about 12)	221	247	0.5	1.6
Oysters—farmed (about 9)	195	119	0.4	1.8
Oysters—farmed, raw (about 6)	160	113	0.3	1.3
Perch (Atlantic)	88	230	0.3	1.8
Pollock—Atlantic	11	383	0.5	1.1
Pollock—walleye	157	241	0.4	1.0
Rockfish	154	223	0.4	1.1
Salmon—Atlantic, farmed	587	1238	1.8	10.5
Salmon—Atlantic, wild	349	1215	1.6	6.9
Salmon—Coho, farmed	347	140	1.1	1.0

Salmon—Coho, wild	341	559	0.9	3.1
Salmon—sockeye, canned, drained	418	564	1.0	6.2
Sardines—Pacific, canned in tomato sauce, drained	520	845	1.4	1.2
Sardines—Atlantic, canned in oil	402	432	0.8	9.1
Scallops—raw (about 6 large)	16	92	0.2	0.7
Scallops—breaded and fried (about 6 large)	13	88	0.2	9.3
Shrimp (about 16 large)	145	122	0.3	0.9
Swordfish	111	579	0.1	4.4
Tilefish	146	623	0.8	4.0
Trout—rainbow, farmed	284	697	1.0	6.1
Trout—rainbow, wild	398	442	0.8	4.9
Trout—mixed species	220	575	0.8	7.2
Tuna—bluefin	309	910	1.3	5.3
Tuna—canned in water, drained	198	535	0.1	2.5
Tuna—skipjack	11	201	0.3	1.1
Tuna—yellowfin	40	191	0.2	1.0
Tuna—light, canned in water, drained	40	190	0.2	0.1
Tuna—canned in oil, drained	23	86	0.1	1.0
Whiting	241	200	0.4	1.4

^aFor general health, aim for 7 to 10 g of omega-3s weekly.

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

SOURCE: U.S. Department of Agriculture's National Nutrient Database for Standard Reference, Release 15 (available free at <http://www.nal.usda.gov/fnic/foodcomp/Data/SR15/sr15.html>). EPA content is listed in this database as 20:5 n-3 and DHA as 22:6 n-3; DHA values not available for all foods.

Chasteberry

Chasteberry (*Vitex agnus castus*) is a botanical with a long history of use for "menstrual disorders." Many small studies have shown promising results, and one larger study examined the effectiveness of chasteberry on PMDD (19,20,21). In this randomized controlled trial, the active arm received 20 mg of chasteberry daily. Compared with placebo, the patients

receiving chasteberry had a significant improvement in the combined symptom score (21). A multicenter noninterventional trial examined the experience and tolerance of chasteberry in 1,634 patients. After use in three cycles, 93% of women reported a decrease in or cessation of symptoms, and 94% of patients reported good or very good tolerance to this botanical. Adverse drug reactions were suspected by physicians in 1.2% of patients, but there were no serious adverse reactions (22). A randomized, single-blind trial comparing *Vitex* and *fluoxetine* showed equal symptom reduction at 2 months (58% and 68%, respectively) (23). Because chasteberry contains iridoids and flavonoids, the mechanism of action is believed to be stimulation of dopamine D₂ receptors, which decrease prolactin levels. *In vitro*, it also inhibits opioid, mu, and kappa receptors. It has no effect on luteinizing hormone or follicle-stimulating hormone levels (24). *Vitex* has also been shown to restore progesterone levels and in Germany is used to treat menstrual irregularities as well as undiagnosed infertility. No significant toxicities have been reported with *Vitex* extracts when used in appropriate dosages.

St. John's Wort

St. John's wort (*Hypericum perforatum*) is recognized as an effective antidepressant for the treatment of mild to moderate depression. One open trial of 19 women found that this compound, when used at a dose of 300 mg per day of a 0.3% hypericin standardized extract, showed a 51% improvement in mood disturbances in PMS/PMDD (25). This dose is one third of that typically used for depression. Although adverse reactions

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occur less frequently than with prescription antidepressants, care must be exercised with the use of this product. Most common side effects include gastrointestinal upset, headache, and agitation. Rare but severe phototoxicity also has been reported. Because St. John's wort induces the cytochrome P450 complex, significant drug interactions can occur. Specifically, reduced levels of birth control pills, *theophylline*, *cyclosporine*, and antiretroviral drugs have been reported. Interactions have also been described with *bupirone*, statins, calcium channel blockers, *digoxin*, and *carbamazepine*. There are no apparent significant interactions with *Coumadin*. The mechanism of action for its efficacy in the treatment of PMS has not been elucidated. There have been two isolated reports of pregnancy occurring in women who were taking oral contraceptives in conjunction with St. John's wort. If patients choose to take St. John's wort, they may want to use a backup method of birth control or change to a different method.

Ginkgo

Ginkgo (*Ginkgo biloba*) has traditionally been used to relieve breast tenderness and discomfort, improve concentration, and enhance sexual function. Its vascular effects, particularly with regard to dementia and peripheral vascular disease, also have been studied. One large study examined the effectiveness of ginkgo in the treatment of women with PMS and found that after two cycles with treatment, breast symptoms were significantly improved in the ginkgo group. The effectiveness in terms of concentration or libido was not examined (26). In doses ranging from 60 to 240 mg of standardized extract per day, ginkgo has shown clinical efficacy in the treatment of breast pain, tenderness, and fluid retention. In at least one study, ginkgo has also been found to be effective in the relief of symptoms related to emotional distress (27). Ginkgo has been promoted as an agent that can increase libido, but the methodology of these studies has been criticized, and further studies are required to better define the botanical's role in these areas. Side effects include gastrointestinal upset and headache. High doses can cause nausea, vomiting, diarrhea, restlessness, or insomnia. Ginkgo also has anticoagulant activity, and care must be taken when used with anti-inflammatory drugs as well as with *warfarin*. The underlying mechanism of action is believed to be dilation of vessels and increased blood flow.

Other products that are used to treat symptoms of PMS and PMDD but are not recommended are listed in Table 13.8.

**Table 13.8 Other Products Often Used to Treat Symptoms of PMS And PMDD
(Not Recommended)**

• **Tryptophan**, an amino acid that is a precursor of serotonin, has been shown in several trials to improve the symptoms of PMS and PMDD. Impurities in one product made in Japan have been associated with the development of eosinophilia–myalgia syndrome (EMS), which can be fatal. It is unclear if all the cases were related to impurities or if some were related simply to the active ingredients. Until this is clearly understood, tryptophan should be avoided.

• **Dehydroepiandrosterone (DHEA)**, a hormone secreted by the adrenal glands and often used for depression, has not been shown to be of benefit in PMS/PMDD.

• **Melatonin**, a hormone that regulates sleep–wake cycles and often is used to prevent jet lag, has been used for the treatment of PMS. There is no evidence of efficacy, and it can worsen depression in some patients.

•**Black cohosh (*Cimicifuga racemosa*)** has been well studied in the treatment of menopausal symptoms, but it has not been studied in the treatment of PMS/PMDD. Although it may prove to be beneficial, data are needed.

•**Evening primrose oil** is frequently used for PMS, but with the exception of cyclic mastalgia, research has failed to show benefit beyond placebo.

•**Dong quai** is an oriental herb often used in combination with other herbs for the treatment of menstrual disorders and menopausal symptoms. Its effectiveness has not been researched.

•**Kava** has been used to treat anxiety and irritability, and several studies have documented its effectiveness. It has, however, been associated with hepatotoxicity, even necessitating liver transplant. It is unclear whether this effect was related to drug or alcohol interactions, contaminants, or the kava itself.

PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder.

Table 13.9 Findings on Alternative Treatments^a

•**Magnesium** Three small trials were included that compared magnesium with placebo. Overall, magnesium was more effective than placebo for pain relief, and the need for additional medication was lessened. There was no significant difference in the number of adverse effects experienced.

•**Vitamin B₆** One small trial showed vitamin B₆ to be more effective at reducing pain than both placebo and a combination of magnesium and vitamin B₆.

•**Vitamin B₁** One large trial showed that vitamin B₁ was more effective than placebo in reducing pain.

•**Vitamin E** One small trial comparing daily vitamin E with *ibuprofen* taken during menses showed no difference in pain relief.

•**Omega-3 fatty acids** One small trial showed fish oil to be more effective than placebo in pain relief. A number of studies have found that the intake of marine origin omega-3 fatty acids (such as salmon and sardines) decrease symptoms of dysmenorrhea. Given the established benefits of omega-3 fatty acids in other conditions such as heart disease, high intake of these compounds can be recommended throughout the cycle.

^aAdapted from **Proctor ML, Murphy PA**. Herbal and dietary therapies for primary and secondary dysmenorrhea. *Cochrane Database Syst Rev* 2003; 1.

Dysmenorrhea

Although dysmenorrhea is in general managed more effectively than PMS and PMDD with conventional approaches, treatment still has a failure rate of approximately 20% to 25%, and many patients seek alternatives. Table 13.9 lists findings by a Cochrane review study on alternative treatments. **The review concluded that vitamin B₁ is effective in the treatment of dysmenorrhea when taken at 100 mg daily, although this finding is based on only one large randomized controlled trial** (28). The results further suggested that magnesium is a promising treatment, but it is unclear what dose or treatment regimen should be used (28). The addition of fish oils has shown promising results.

Manipulative and Body-based Methods

Premenstrual Symptoms

Massage has been shown to relieve anxiety, sadness, and pain immediately after the therapy, but it has not been shown to reduce symptoms of PMS/PMDD overall.

Chiropractic manipulation has not been shown to be of benefit for women with PMS/PMDD. One small (N = 25) placebo-controlled crossover study showed the group receiving chiropractic treatment had a significant improvement in symptoms, but the group that received placebo first improved over baseline with the placebo but experienced no further improvement when they received the active treatment (29).

Dysmenorrhea

A Cochrane review of the use of spinal manipulation for primary and secondary dysmenorrhea concluded that overall there is no evidence to suggest that spinal manipulation is effective in the treatment of primary or secondary dysmenorrhea. In four trials, high-velocity, low-amplitude manipulation was no more effective than sham manipulation, although it was possibly better than no treatment (30). Three of the smaller trials indicated a difference in favor of the manipulation; however, the one trial with sufficient sample size found no difference. There was also no difference in

adverse effects between the two groups (30).

Mind-body Interventions

Relaxation techniques have shown some very promising results for women with PMS/PMDD. One study examined the effect of the relaxation response for 15 minutes, twice a day, for 3 months, compared with women who read for the same amount of time, and women who charted their symptoms. Of women in the relaxation response group, 58% experienced improvement in their symptoms, compared with 27% for the reading group, and 17% for the charting group (31). Given that there are many other health benefits to the relaxation response, with no cost and no risk, it is a good technique to recommend to patients.

Alternative Medical Systems

Oriental Medicine and Acupuncture

Oriental medicine and acupuncture have been used traditionally for thousands of years for a myriad of menstrual symptoms, PMS and PMDD among them. The effectiveness in this domain has not been studied to date. There have been studies showing the effectiveness of acupuncture in the treatment of mild depression and generalized anxiety, although not all results have been positive. In general, if the patient has access to a qualified acupuncturist and has a belief or interest in pursuing this therapy, it is generally safe and may be effective. She should be informed, however, of the lack of research in this domain.

There has been one small but methodologically sound trial of acupuncture in the treatment of primary dysmenorrhea. This trial followed 43 women for 1 year and showed significant effectiveness of acupuncture when compared with placebo (91% of women showed improvement, compared with 10% to 36%, 18%, and 10% in the other groups) (28). Clearly more research is needed, but this is a promising and safe modality.

Homeopathy

The use of homeopathy in the treatment of PMS and PMDD has not been well studied, nor has its effectiveness in the treatment of related disorders such as depression or anxiety. One study

did claim positive results but was fairly weak in design as well as in showing improvement (31).

Infertility

Mind-body Interventions

Mind-body approaches are of particular interest in the infertility patient. Not only are the treatments for infertility stress inducing, but increased stress is associated with decreased fertility (as well as increased risk of such things as gestational diabetes, preterm labor and delivery, and prolonged labor).

In a study of infertility patients, two group psychological interventions were compared with routine care. The two groups who received group support and cognitive behavioral therapy had fertility rates of 54% and 55%, respectively, compared with the control group, which had a pregnancy rate of 20%. There were, however, large and disparate dropout rates, which complicate the interpretation of these results (32). Intercessory prayer has been explored in a double-blind, randomized controlled trial. Patients undergoing *in vitro* fertilization in Korea (N = 219) were randomized to receive prayer-by-prayer groups in the United States, Canada, and Australia. The group that received the intervention had a pregnancy rate of 50% compared with the control group rate of 26% ($p = 0.0013$) (33).

In general, mind-body therapies, such as relaxation techniques and hypnosis, are reasonable to recommend to relieve a wide variety of issues that can arise with infertility patients.

Alternative Medical Systems

The use of acupuncture has also been studied in the treatment of infertility. Auricular acupuncture was studied as an alternative therapy for female infertility secondary to oligomenorrhea or luteal insufficiency, and the authors concluded it was a valuable therapy (34). Another study used electroacupuncture in anovulatory women with PCOS and found that regular ovulation was induced in more than one third of the women. **In a randomized controlled trial comparing usual care to usual care plus 25 minutes of a standard acupuncture treatment pre- and postembryo transfer, the pregnancy rates were 43% in the intervention arm as opposed to 26% in the control arm.**

The acupuncture protocol was designed to promote sedation, uterine relaxation, and increased uterine blood flow (35). It is interesting to note that blood flow impedance in uterine arteries, measured as the pulsatility index, has been considered useful in assessing endometrial receptivity to embryo transfer. A study was performed assessing the effect of electroacupuncture on the pulsatility index of infertile women. After treatment twice a week for 4 weeks, the mean pulsatility index was significantly reduced both shortly after the last treatment and also 10 to 14 days after the treatments. The skin temperature of the forehead also was increased significantly, suggesting a central inhibition of sympathetic activity (36).

Menopause

Before the release of the results of the Women's Health Initiative, 80% of women in the United States were using "nonprescriptive therapies" to help manage their menopausal symptoms, and many of these therapies were CAM approaches. In a study exploring women's beliefs about "natural hormones," women using compounding pharmacies believed that compared with standard hormones, natural hormones are safer, cause fewer side effects, and are equally or more effective for symptom relief. Many women believed natural hormone therapy was equally or more effective for long-term protection of bones and lipid levels (37). It is reasonable to assume that women are now exploring and choosing such therapies in ever increasing numbers, often without being accurately or fully informed. This expanded market generates more products and promotion of alternatives. It is imperative that physicians be informed about these options so they can help patients make medically sound choices.

Biologically Based Therapies

The list of botanicals promoted and used for the treatment of menopausal symptoms is extensive. Following is a review of the products most commonly used and recommended based on research evidence.

Vitamin E

Since the 1940s, vitamin E has been studied for the treatment of hot flashes. Although some early studies showed promising results, more recent studies evaluating 200- to 600-IU doses have failed to show an effect. Up to 1,200 IU may be needed to see an effect. Vitamin E is an anticoagulant, and spontaneous subarachnoid hemorrhages have been reported. One study examining vitamin E in menopausal patients with breast cancer found that after 4 weeks

of 800 IU daily, the patients in the treatment arm had on average one less hot flash per day. Although this finding was statistically significant, it was not significant clinically (38).

Black Cohosh

Premenstrual Symptoms and Menopause

Black cohosh (*Cimicifuga racemosa*) has traditionally been used for relief of both PMS and menopause symptoms. It has been used in the Native American population for centuries and in Germany since 1950. Its most studied form is a brand called *Remifemin*, which is standardized to 1 mg of *deoxyactein* and is administered in a dose of 40 mg two times daily. Most early studies had been uncontrolled,

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but recent studies have been more methodologically sound. Initially, it was felt that black cohosh was estrogenic. Subsequently, it has been shown that it does not contain phytoestrogens and that it does not have an estrogenic effect on vaginal cytology. Additionally, there are no changes in hormone levels in women taking black cohosh. Studies confirmed that black cohosh inhibited luteinizing hormone in ovariectomized rats, as well as in women. Animal studies showed no uterotrophic or vaginotropic activity. Luteinizing hormone, therefore, is most likely being decreased via neurotransmitters. In laboratory studies, black cohosh actually suppresses rather than stimulates breast cells (39). One of the first randomized controlled trials on black cohosh was done in 1987. It included 80 women who were randomized to 0.625 mg of *Premarin* versus 8 mg of black cohosh versus placebo for 12 weeks. The group taking black cohosh showed significant improvement in menopausal symptoms, anxiety, and vaginal dryness, and it was well tolerated (40). Another study done in 1987 compared estrogen injections with black cohosh. In this study, 82% of women reported good to very good relief of their symptoms, with no side effects noted (41). In 1988, another study compared *conjugated estrogens*, *estrogen-gestogen* sequential therapy, *estriol*, and black cohosh. The results with black cohosh were comparable to those of the hormonal therapies (42). In a study of 629 women who underwent 6 to 8 weeks of treatment with black cohosh, 80% of women had improvements in hot flashes, fatigue, irritability, and vaginal dryness. At 8 weeks, 50% of women were symptom free (43). Another randomized controlled trial of black cohosh compared 40 mg with 127 mg a day for 6 months. Luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, prolactin, estradiol, and vaginal dryness were not affected. Both dosages had similar

effectiveness and safety (44). In a recent double-blind, placebo-controlled trial, black cohosh (40 mg) was compared with conjugated estrogen (0.6 mg) and placebo in 62 women for 3 months (45). Black cohosh was found to be equally potent to conjugated estrogen and superior to placebo in decreasing symptoms. Both black cohosh and conjugated estrogen had beneficial effects on bone metabolism, as evidenced by bone-specific alkaline phosphatase. Black cohosh had no effect on endometrial thickening, as measured by vaginal ultrasonography, unlike conjugated estrogen, which caused a significant increase in endometrial thickening. Additionally, an increase in vaginal superficial cells occurred with both black cohosh and conjugated estrogen. The authors proposed that black cohosh contains selective estrogen receptor modulator activity. In a randomized double blind trial comparing the efficacy of black cohosh to placebo, black cohosh was found to be effective in reducing symptoms of menopause. The effect was similar to that of hormone therapy and was most significant in women in the early stages of menopause (46).

Although many of the studies of black cohosh have design weaknesses, it appears to be safe and efficacious for the treatment of menopausal symptoms. Therapy should begin at 20 to 40 mg two times daily, standardized to 2.5 triterpenes. Others have recommended a dose of 40 to 200 mg daily. Patients should be informed that it might take 4 to 8 weeks to see an effect. Side effects are rare and include gastrointestinal upset, headache, weight gain, and dizziness. Some recommend using black cohosh for no longer than 6 months (47). There is no indication that longer use is unsafe, and studies following patients for 2 years are ongoing.

Breast Cancer

Multiple studies have shown that black cohosh has an inhibitory effect on estrogen receptor breast cancer cells. One study showed augmentation of the antiproliferative effects of *tamoxifen*. In a study that looked at the effectiveness of black cohosh in reducing menopausal symptoms for breast cancer patients, both the placebo group and the group receiving black cohosh had a 27% reduction in the number and intensity of hot flashes. Only sweating was significantly more improved in the black cohosh arm (47). In another study, 136 breast cancer survivors were randomized either to *tamoxifen* alone or *tamoxifen* plus black cohosh. At 6 months, there were no significant differences, but at 1 year, 47% of women in the intervention arm versus none in the control group were free of hot flash. Severe hot flashes were also reduced in the intervention arm (24%) compared with the *tamoxifen*-alone arm (74%) (48). Although it is useful to know that

black cohosh is not estrogenic, its efficacy in this group of patients has not yet been established.

Ginseng

Many different botanicals use the name *ginseng*. The two most common are Siberian ginseng (*Eleuthero*) and oriental or Korean ginseng (*Panax*). Both of these agents are extracted from the root of their respective plants, and both are used to combat fatigue or to restore "vital force" for performance enhancement.

Panax ginseng is a small perennial that grows in northeast Asia. One study of 12 patients examined its effect on menopausal women, both with and without the symptoms of fatigue, insomnia, and depression. At baseline, the patients with symptoms had significantly higher anxiety states. The dehydroepiandrosterone-sulfate was one half that of those in the control group, and the cortisol/dehydroepiandrosterone-sulfate ratio was significantly higher in the symptomatic patients. After treatment, the anxiety state decreased to that of the controls, and the cortisol/dehydroepiandrosterone-sulfate ratio decreased significantly although not to the level of the control group (49).

In terms of the physiologic symptoms, a randomized, multicenter, double-blind parallel group study compared a standard ginseng extract with placebo. Quality of life and physiologic parameters were assessed at baseline and after 16 weeks of treatment. There was no significant difference in symptom relief and no significant difference in the physiologic parameters of follicle-stimulating hormone, estradiol, endometrial thickening, maturity index, or vaginal pH. Patients did, however, experience significant improvement in depression, sense of well-being, and health (50).

There is no evidence to support the use of ginseng for relief of physiologic symptoms.

If patients are suffering from psychological symptoms of menopause, they potentially may benefit from *Panax ginseng*. Although its mechanism of action is not clear, *Panax ginseng* does not appear to be estrogenic. Use of *Panax ginseng* should be avoided with stimulants, and it may cause headaches, breast pain, diarrhea, or bleeding. The recommended dose is 100 mg of a standardized extract two times daily for 3 of 4 weeks.

The estrogenic effect of black cohosh, dong quai, ginseng, and licorice root has been evaluated by (i) an examination of the effect on cell proliferation of MCF-7 cells (a human breast cancer cell line), (ii) transient gene expression assay, and (iii) a bioassay in mice. The authors concluded that dong quai and ginseng stimulate growth of MCF-7 cells independent of estrogenic activity, and that black cohosh and licorice root neither have estrogenic activity nor stimulate the breast

cell line (39).

Red Clover

Red clover (*Trifolium pratense*) is a member of the legume family, with brand names including *Promensil* and *Rimostil*. It contains at least four estrogenic isoflavones and, therefore, is promoted as a source of phytoestrogens. Red clover is a medicinal herb with no traditional long-term use in menopause. Its estrogenic effects were first discovered by observing its effects on sheep. The term *Clover syndrome* is used to describe the symptoms frequently seen in sheep that consume large amounts of red clover. **This syndrome is characterized by reproductive complications, including infertility.** Despite its estrogenic activity, several studies, including two double-blind placebo-controlled trials, have failed to show an effect over placebo in the treatment of menopausal symptoms (51). A randomized controlled trial of 30 women compared the effect of red clover versus placebo on hot-flash frequency. All patients received placebo for 4 weeks and then were randomized to 80 mg of red clover versus placebo for 12 weeks. In the first 4 weeks, hot flashes were reduced by 16% and subsequently further reduced by 44% in the red clover group

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compared with no further reduction in the placebo group ($P < 0.01$) (52). In a much larger trial involving 252 women, two different red clover supplements were compared with placebo over 12 weeks (*Promensil*, containing 82 mg isoflavones, and *Rimostil*, containing 57 mg isoflavones). Although *Promensil* did reduce hot flashes more quickly than *Rimostil* or placebo, all three groups experienced the same level of reduction in hot flashes at the end of 12 weeks. This study does supply some evidence for a biological effect of *Promensil*, but neither of the red clover supplements had a clinically significant effect when compared with placebo (53). In one randomized controlled pilot study examining the effect of red clover on the endometrium, an antiproliferative effect was not observed (54). The effect of red clover on the endometrium must be further delineated.

Other trials have examined the efficacy of red clover in moderating cardiovascular risk factors. Of five trials examining the effect of red clover on lipid levels, three showed no effect, and one had insufficient data to interpret. Another trial examined the effects of red clover on arterial compliance and showed significant improvement (23%) when compared with placebo. There was no effect on lipids. One intervention-only trial using a preparation of *Rimostil* found a significant increase in high-density lipoprotein, a decrease in apolipoprotein B, and an increase in cortical bone in the radius and ulnar after 6 months of treatment (55,56).

Red clover has no traditional long-term history of use in menopause. It has no clear demonstrable effect on symptoms of menopause, it is estrogenic, and its effects on breast and endometrium have not been adequately studied. Coumarin is present in some clover species. Unfortunately, brands of red clover such as *Promensil* are being marketed directly to patients. For the reasons stated, red clover is not recommended.

Dong Quai

Dong quai (*Angelica sinensis*) has a long history of traditional use in menopause and in the treatment of menstrual problems. Traditionally, in the oriental system of medicine, it is used in combination with other botanicals. Several studies of the effectiveness of dong quai in treating the symptoms of menopause have failed to show its effectiveness (57). No evidence exists to support the use of dong quai as a single agent in the treatment of menopausal symptoms. The use of dong quai in combination with other herbs, as has been done traditionally, has not been well studied. It is important to note that dong quai also contains coumarin derivatives.

Kava

Kava (*Piper methysticum*) is native to the South Pacific, and one of its traditional uses is to reduce anxiety. It is often recommended for menopausal symptoms, particularly irritability, insomnia, and anxiety. Studies have shown that 100 to 200 mg, three times daily, standardized to 30% kavalactones, decreases irritability and insomnia associated with menopause. It often is used in combination with other components, such as black cohosh and valerian, for the management of menopausal symptoms. One study that examined the use of kava in addition to hormone therapy for the treatment of anxiety showed that the combined use resulted in a significant decrease in anxiety when compared with hormone therapy alone.

Kava, however, has the potential for significant, albeit rare, side effects. Cases of hepatotoxicity severe enough to require transplant have been reported. Other side effects include dermatitis, as well as a movement disorder similar to Parkinson's disease but reversible. The use of kava is not recommended, but if patients are using this botanical (which is available over the counter), they should be informed of the risks, as well as advised to avoid taking kava in conjunction with other anxiety-reducing agents or with alcohol.

St. John's Wort (*Hypericum perforatum*)

The leaves and the tips of the flowers of the plant St. John's wort (*Hypericum perforatum*) have been used medicinally, primarily as an antidepressant. It is also used for anxiety, and in Germany, it is used to treat menopausal mood swings.

Although its mechanism of action is unclear, St. John's wort does appear to be beneficial in relieving mild to moderate depression, with 60% improvement in mood, energy, and sleep with a dose of 300 mg three times daily. Standardization is controversial because the active ingredients have not been identified, but most research has been done on products standardized to 0.3% hypericin. The first trial to examine its use for menopausal symptoms was done in 1999. Patients not taking hormone therapy were given 300 mg of St. John's wort three times daily, and symptoms were evaluated at baseline and 5, 8, and 12 weeks by both patients and physicians. At baseline, 80% to 90% of all symptoms were moderate to marked in severity. By 12 weeks, 20% to 30% remained at this level, whereas most patients had only slight symptoms or were symptom free. There was no change in vasomotor symptoms; however, 80% of patients reported that their sexuality was substantially enhanced. Of 106 patients, 4 reported adverse effects. These effects included skin rash with sun exposure, gastrointestinal upset, headache, and fatigue (58). St. John's wort induces the cytochrome P450 complex. Specifically, lower levels of oral contraceptives, *theophylline*, *cyclosporine*, and antiretroviral drugs have been reported. Interactions have also been described with *bupirone*, *statins*, *calcium channel blockers*, *digoxin*, and *carbamazepine*. There are no apparent significant interactions with *Coumadin*.

Chasteberry

Chasteberry (*Vitex agnes*) has a long history of uses by civilizations ranging from Greeks to the monks of medieval times. Among the uses is treatment of menopausal symptoms. Although its use has been recommended for this indication, the efficacy of chasteberry in menopause has not yet been demonstrated.

Ginkgo Biloba

Ginkgo biloba is often promoted for the improvement of libido in menopausal women. Muira puama plus ginkgo had a significant effect in 65% of the patients in one study (59). Side effects include gastrointestinal upset and headaches, and drug interactions can occur with *estrogens*, *statins*, and calcium channel blockers. Ginkgo also has an anticoagulant effect.

Mind-body Interventions

Mind–body therapies for the treatment of menopausal symptoms have been studied in several domains. In one randomized controlled trial, symptomatic menopausal patients who had at least five hot flashes per 24 hours were randomized to either the relaxation response, to reading, or to a control group. The relaxation response group had significant reductions in hot-flash intensity, tension–anxiety levels, and depression compared with the control group, which had no significant changes (60). In another randomized controlled trial of symptomatic menopausal patients, women with frequent hot flashes were randomized to paced respiration, muscle relaxation, and alpha-wave feedback. In the paced respiration group, there was significant reduction in the hot-flash frequency, whereas muscle relaxation and biofeedback showed no differences. The proposed mechanism of action is decreased central sympathetic activity (61).

Insomnia, which is another frequent symptom of menopause, is a complex, multifactorial problem. Optimal treatment has been described as incorporating the following components: stress management, coping strategies, enhancement of relationships, as well as lifestyle changes that facilitate sleep (62).

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Overall, mind–body techniques are a low- or no-cost, low-risk intervention that can decrease central nervous system adrenergic tone. These techniques have been reported to decrease hot flashes and other menopausal symptoms significantly.

Alternative Medical Systems

Oriental medicine has been used for more than 2,500 years and includes treatment with acupuncture, herbs, and movement. Although diagnosis and treatment is highly individualized, from the perspective of oriental medicine, menopause is often associated with deficiencies in qi, blood, and jing. Acupuncture is one of the best-studied CAM modalities, but more studies of higher quality are needed regarding its application to the menopausal patient. One uncontrolled study, which explored the experience of more than 300 women, found that 97% of women reported that acupuncture improved their symptoms, and 51% reported being symptom free (63). In a pilot study looking at the use of acupuncture in patients being treated with *tamoxifen*, 15 patients were followed for 6 months. Patients were evaluated before and after 1, 3, and 6 months of treatment. There was significant improvement in

anxiety, depression, and somatic and vasomotor symptoms. Libido was not affected. This is a promising area for those patients whose options for treatment of these symptoms are limited.

In the hands of a competent practitioner, acupuncture is a safe CAM modality. If menopausal patients are interested in exploring this technique as part of their plan for managing symptoms and understand the lack of comprehensive studies, it is reasonable to support a trial of acupuncture with a qualified practitioner. Because many of the herbal treatments in oriental medicine can be estrogenic, it is best to avoid them if the patient is taking any form of hormonal therapy.

"Natural" Hormones

There is increasing confusion around the myriad hormonal options for patients. Because many hormonally active compounds are available over the counter, physician awareness about these issues is essential, especially in light of the findings of the Women's Health Initiative.

Natural Versus Bioidentical Hormones

There is a dominant belief in the culture that natural is "good" and synthetic is "bad." A natural product is any product with principle ingredients that are of animal, mineral, or vegetable origins. Natural products may have no resemblance to the ingredients in their natural state. For example, conjugated equine estrogens are natural products. They do not, however, resemble anything natural or native to the human body. It is useful to make this distinction with patients. Very often patients requesting "natural hormones" are uncertain about what they are actually requesting. Most patients, when using this term, are looking for bioidentical hormones, or hormones that are molecularly identical to the hormones their ovaries produce.

The ovaries produce three types of estrogen: 17 beta-estradiol, estrone, and estriol. Premenopausally, the predominant estrogen produced by the ovary is 17-beta estradiol, or E₂. It is converted back and forth to estrone, E₁, which also is made in the fat and, therefore, is the predominant estrogen postmenopausally. All of the patches, as well as several oral formulations such as *Estrace*, are E₂. When E₂ is taken orally, much of it is converted to E₁ in the gut. E₁ and E₂ essentially are equivalent in their level of estrogenic activity. Estriol, E₃, is the weakest of the three estrogens and is predominantly made in the placenta during pregnancy. It has not been conventionally prescribed and currently is available only through

compounding pharmacies. *Estriol* is the predominant form of estrogen in *Tri-Est* and *Bi-Est*. *Estriol*, *Tri-est*, and *Bi-est* are frequently used and recommended by the alternative medicine community.

Conjugated equine estrogens are composed of more than 10 different molecules extracted from the urine of pregnant mares. This is a natural product but is not bioidentical or native.

In addition to animal conjugated equine estrogen, a synthetic version, such as *Cenestin*, is available.

Table 13.10 Reasons for Difficulty in Drawing Conclusions Regarding Use of Hormones

Drawing conclusions regarding options for the use of these hormones is challenging for a variety of reasons:

1. It is essential to reinforce to patients that all hormones are not created equal.

Different hormones have different effects. For example, estriol is often promoted as a hormone that does everything that conjugated equine estrogen does but with none of the risks. Given that it is a significantly weaker estrogen than conjugated equine estrogen, this is dubious and is not based in scientific evidence.

2. Native or bioidentical hormones are rarely included in research protocols. The Women's Health Initiative studied only conjugated equine estrogen (*Premarin*) and MPA (*Provera*). The Postmenopausal Estrogen-Progestin Intervention (PEPI) used only conjugated equine estrogen, but did compare it with micronized *progesterone* (and showed micronized *progesterone* to be as effective as *medroxyprogesterone acetate* at protecting the endometrium and better than *medroxyprogesterone acetate* at protecting the lipid benefits of estrogen).

3. All forms of hormone therapy frequently are clumped together as one entity.

The distinctions between the types of hormones studied are rarely made in the media and often not clear even in the medical literature. The coverage of the Women's Health Initiative is a perfect example, as the media generalized its findings to hormone therapy, and even most information released by and for doctors did not clarify that the findings were regarding one specific form of estrogen combined with one specific form of progestin.

It is difficult to draw conclusions regarding options for the use of these hormones. The reasons for this are listed in Table 13.10.

Bioidentical Hormones

Progestins

Bioidentical *progesterone* is available either through compounding pharmacies or through retail pharmacies as micronized *progesterone*, natural *progesterone*, or *progesterone* USP (brand name *Prometrium*). *Medroxyprogesterone acetate* is a nonbioidentical progestin (i.e., its molecular structure is foreign to the body).

Bioidentical Estrogens

E_2 , or 17 beta-estradiol, often has been used interchangeably with *conjugated equine estrogen*. It is effective in relieving vasomotor symptoms, helps maintain bone, and has been shown to improve the lipid profile. It is most bioidentical when delivered in the form of the patch because its oral form is converted to estrone in the gut. (The patch also bypasses the liver and is not as beneficial in its effects on high-density lipoprotein and low-density lipoprotein, but it increases triglycerides to a lesser extent.) No comprehensive long-term data regarding its use are available.

Estriol, or E_3 , the weakest of the estrogens that occurs naturally only in high circulating levels during pregnancy, is very popular in the alternative community. Unfortunately, it is often promoted as the ideal estrogen, a natural alternative providing all of the benefits of hormone therapy with none of the risks. This assumption is not supported by the literature, as the research to date on *estriol* is limited. In one study examining the use of *estriol* over 12 months, 53 women were given 2 mg daily. They reported good symptom relief and satisfaction, and histologic evaluation of the endometrium revealed no hyperplasia or atypia. Bone mineral density showed no change (64). In another study examining the effect of *estriol*, 64 women were followed for 24 months. There were four treatment arms: 2.0 mg E_3 plus 2.5 mg *medroxyprogesterone acetate*, 0.625 mg of *conjugated estrogen* plus 2.5 mg *medroxyprogesterone acetate*, 1 μ g of 1-alpha hydroxy vitamin D_3 , and 1.8 g calcium lactate containing 250 mg of elemental calcium. Outcome measures were taken at baseline, 6, 12, 18, and 24 months, and included the following assessments: bone mineral density at third lumbar vertebrae, serum levels of osteocalcin, total alkaline phosphatase, and urinary ratios of calcium/creatinine and hydroxyproline/creatinine. The findings

revealed decreased bone mineral density in the vitamin D and calcium groups and no decrease in the *conjugated estrogen* and E₃ groups. Osteocalcin and alkaline phosphate was decreased or without change in the conjugated estrogen and E₃ groups, and was increased in the vitamin D₃ and calcium groups. Urinary calcium/creatinine ratios were decreased with E₃ and conjugated estrogen, and there was no decrease with the use of vitamin D₃ and calcium. Urinary hydroxyproline/creatinine ratios were decreased in the conjugated estrogen group, unchanged in the E₃ and vitamin D₃ groups, and increased in the calcium group. Uterine bleeding was significantly less in the E₃ group compared with the conjugated estrogen group, with 2.4 days compared with 13 days per person. In conclusion, the study supported the finding that a bone-preserving effect occurred with E₃ when compared with *conjugated estrogen* (65).

It has been proposed that *estriol* may have anticarcinogenic activity. Unlike *estradiol*, *estriol* is not carcinogenic in rodent models, reduces uterine growth, and enhances phagocytic activity. After one or more pregnancy, *estriol* excretion significantly increases in comparison with nulliparous women. This may or may not be linked to the increased risk of breast and ovarian cancer in nulliparous women.

In preliminary studies, oral *estriol* appears to provide symptom relief and to stimulate breast and endometrial tissue less than estradiol. It also may prove to have mildly beneficial effects on bone. It appears to exert estrogenic effects on the endometrium and to have no effect or mild effects on lipids. No clinical interventional trials exist on the effect of oral *estriol* use on the breast.

Tri-est and Bi-est

Tri-est and *Bi-est* are formulations in which the predominant *estrogen* is *estriol*. The typical formulations contain 80% *estriol*. Typically *Tri-est* contains 2 mg of *estriol*, 0.25 mg of *estradiol*, and 0.25 mg of *estrone*, and *Bi-est* contains 2 mg of *estriol* and 0.5 mg of *estradiol* (66). It should be noted, however, that these names refer only to the types of *estrogen* used, and the specific amounts of each can vary. These particular formulations are often marketed as the most "natural" form of *estrogen* therapy because they contain either two or all three forms of naturally occurring estrogens. The following factors should be noted:

Tri-est and *Bi-est* are not formulated in naturally occurring ratios or quantities.

- Although *Tri-est* and *Bi-est* are only 20% E₂ or E₂ plus E₃, the dose is still significant (i.e., 0.5 mg).
- Although a certain combination of E₁/E₂/E₃ may prove to have benefits over other forms of hormone therapy and should be explored, this research currently does not exist.

Estriol Vaginal Cream

Estriol vaginal cream has been studied in women who have had recurrent urinary tract infections. This randomized controlled trial compared vaginal *estriol* cream with placebo for 8 months of treatment and showed a significant reduction in urinary tract infections (0.5 versus 5.9 per patient year). In the treatment arm, there was a reduction in vaginal pH from 5.5 to 3.8 compared with no decline in the placebo group (67).

The effect of vaginal *estriol* cream on the endometrium was evaluated in a study examining long-term use for urogenital atrophy. Patients were given 0.5 mg of *estriol* cream vaginally for 21 days, then twice weekly for 12 months. Hysteroscopic and histologic examinations were performed at baseline, 6 months, and 12 months. Complete endometrial atrophy occurred in all patients (N = 23) (68). This pilot study needs to be performed in a larger patient population, but its findings are promising.

Bioidentical Progestins

The Postmenopausal Estrogen-Progestin Intervention (PEPI) trials provided a multicentered, randomized controlled trial that, among other things,

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compared *conjugated equine estrogen* plus *medroxyprogesterone acetate* with *conjugated equine estrogen* plus natural or micronized *progesterone* (69,70). The trial compared 12 days of 10 mg of *medroxyprogesterone acetate* with 200 mg of micronized *progesterone*. The micronized *progesterone* provided equal protection of the endometrium and actually was better at protecting the beneficial effects of the *conjugated equine estrogen* on the lipid profile. Patients reported that micronized *progesterone* had significantly fewer side effects

micronized *progesterone*. Interestingly, the arm of the Women's Health Initiative that was prematurely discontinued was the conjugated equine *estrogen/medroxyprogesterone acetate* arm. The *conjugated equine estrogen*-alone arm was continued. The role and the effect of *medroxyprogesterone acetate* should be closely examined. In ovariectomized rhesus monkeys, E_2 plus *medroxyprogesterone acetate* interfered with ovarian estrogen protection against coronary vasospasm. E_2 plus *micronized progesterone* protected against coronary vasospasm.

Given the increased cardiovascular risks in women taking *conjugated equine estrogen* and *medroxyprogesterone acetate*, combined with the positive data from PEPI, *micronized progesterone* is an excellent choice for patients who are taking systemic estrogen and have a uterus.

Natural *progesterone* has also been used as a single agent in the treatment of menopausal symptoms. The typical dose is 100 mg per day. More research is needed to demonstrate efficacy.

Yam Creams, Progesterone Creams

Yam creams and *progesterone* creams, which are both sold over the counter, are distinctly different products. Yam creams should, by definition, not contain *progesterone*, but rather should contain phytoprogestones, plant products that are *progesterone*-like (Table 13.11). *Progesterone* creams, by contrast, should contain progesterone. Part of the challenge is that there is a large media presence asserting that *progesterone* creams can solve all that ails menopausal women. These creams are not regulated by the FDA. Their content is highly variable, ranging from 700 mg *progesterone*/ounce to less than 2 mg/ounce in products whose names imply that they are progesterone creams, not yam creams. The absorption of these products also is highly variable.

Table 13.11 Progesterone and Wild Yam Creams

400–700 mg progesterone per ounce	Pro-Gest Bio Balance Progonol Ostaderm Pro-Alo
2–15 mg progesterone per ounce	PhytoGest Pro-Dermex Endocrema Life Changes Yamcon Wild Yam Extract PMS Formula Menopause Formula Femarone-Nutri-Gest
Less than 2 mg progesterone per ounce	Progerone Wild Yam Cream Progestone-HP

Wild yam creams (which refer to the genus name *Dioscorea villosa*, rather than the fact that they are grown in the wild) are applied topically. They contain steroidal saponins, including diosgenin, and claim to affect estrogen steroidogenesis. Although these are interesting products, studies of their safety and efficacy are needed. In one double-blind, placebo-controlled crossover study, after a 4-week baseline period, patients received 3 months of active treatment and 3 months of placebo. Symptom diaries were maintained at baseline and then for 1 week of each month. Blood and salivary hormone levels as well as serum lipids were assessed at baseline, 3 months, and 6 months. At 3 months there were no significant side effects and no change in levels of blood pressure, weight, lipid levels, follicle-stimulating hormone, glucose, estradiol, or progesterone. In terms of symptom relief, the placebo and yam cream had a minor effect on the number and severity of flushes. Although wild yam creams appear to be free of side effects, they also appear to have little effect on menopausal symptoms (71).

In terms of *progesterone* creams, a randomized controlled trial was performed comparing transdermal *progesterone* with placebo. One quarter teaspoon of 20 mg of

progesterone was used daily for 12 months. In addition, all patients took a multivitamin plus 1,200 mg of calcium. Outcomes evaluated included DEXA results, serum thyroid-stimulating hormone, follicle-stimulating hormone, lipids, chemistry, and symptom diary. The group that received the progesterone cream reported 83% improvement in hot flashes compared with 19% improvement in the placebo group. There was no difference in bone density (72).

Given the data currently available, *progesterone* or *yam* creams should not be considered adequate to protect the uterus in a woman taking systemic estrogen. *Progesterone* cream may be useful for symptom relief in women not taking systemic hormone therapy, and it may prove to have other benefits and risks.

Counseling Patients

It's important to communicate to patients what is known regarding hormone therapy as well as what is not known. Some of the unknown aspects of hormone therapy are listed in Table 13.12.

Given the present state of the medical knowledge, the need to individualize treatment plans in menopausal women cannot be overemphasized. It is essential to clarify patient goals, as well as individual health risks, history of hormonal exposure (both length and time), family history, and personal preferences.

Table 13.12 Unknown Aspects of Hormone Therapy

- The risks and benefits of bioidentical hormone therapy (i.e., how the results of the Women's Health Initiative translate to bioidentical hormones)
- The role of *medroxyprogesterone acetate* in increasing certain risks
- The long-term risks and benefits of estriol
- The effects of different doses of hormones
- The correlation of circulating hormone levels to different doses, and the correlation of different hormone levels to risks and benefits
- The effect of lifelong hormonal exposure
- The risks and benefits of hormone therapy when initiated at the age of menopause

Surgery and CAM

There are special considerations regarding CAM and the surgical patient. These issues primarily fall into two domains:

- Supplements that, when used perioperatively, may affect the patient's course
- CAM approaches that may be of benefit to the surgical patient

When examining what patients are using that may affect their surgical course, the greatest concern and awareness needs to be in the domain of biologically based therapies. A survey of 2,560 surgical patients in five California hospitals revealed that 68% of patients were using botanicals, 44% of them did not consult their physician, 56% did not inform their anesthesiologists, and 47% did not stop them before their surgery. Variables that were associated with use included female sex, age 35 to 49 years, higher income, Caucasian race, higher education, and problems with sleep, joints, back, allergies, and addiction (73). A survey based in a tertiary care center examined the use of botanicals and vitamins in patients preoperatively (N = 3,106). Of the patients studied, 22% were using botanicals and 51% were using vitamins. The typical users were women and in the age range of 40 to 60 years. The most commonly used compounds were echinacea, ginkgo biloba, St. John's wort, garlic, and ginseng (74). In another study based in a university medical center that surveyed patients undergoing outpatient surgery, 64% of patients were using supplements: 90% of them were using vitamins, 43% were using garlic extracts, 32% ginkgo biloba, 30% St. John's wort, 18% ma huang, 12% echinacea, and others were using aloe, cascara, and licorice (75).

Effects on Surgery

Many of the most commonly used substances have effects of which surgeons and anesthesiologists should be aware. Botanicals used with anesthesia can lead to the following complications:

-

Prolongation of anesthetic agents

- Coagulations disorders
- Cardiovascular effects
- Electrolyte disturbances
- Hepatotoxicity
- Endocrine effects

Prolongation of Anesthetic Agents

Valerian, kava, and St. John's wort are among the more commonly used botanicals that can prolong the effects of anesthetic agents. Valerian has sedative effects that are believed to be mediated by *benzodiazepine* and GABA receptors. For patients who use valerian on a daily basis, it is suggested that it be tapered off over the weeks preceding the surgery. Kava is mediated by GABA receptors and potentiates the sedative effects of anesthetics. The general recommendation is to discontinue its use 24 hours before surgery. St. John's wort induces cytochrome P450 enzymes (*cyclosporin*, *indinavir*, and *warfarin*). It modulates the GABA receptor and inhibits the reuptake of serotonin, dopamine, and noradrenaline. The recommendation is to discontinue it 5 days preoperatively.

Coagulation Effects

Some of the more commonly used supplements and botanicals that have been reported to have anticoagulative properties include fish oil, ginseng (Asian and American), ginkgo, garlic, vitamin E, ginger, feverfew, dong quai, and chondroitin.

Licorice root contains glycyrrhizic acid, which has an aldosteronelike effect and can result in hypertension, hyperkalemia, and edema. Ma huang (ephedra) has been associated with arrhythmias and hypertension, and ginseng also has been associated with hypertension.

Electrolyte Disturbances

Licorice root has been associated with hypernatremia and hypokalemia. Goldenseal can reduce the effect of antihypertensives.

Hepatotoxicity and Endocrine Effects

The following botanicals have been associated with hepatotoxicity: kava, red yeast rice (which contains lovastatin), chaparral, valerian, and echinacea. In terms of endocrinologic effects, both chromium and ginseng can cause hypoglycemia. Table 13.13 highlights

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some of the more commonly used botanicals and vitamins and their possible effects in the surgical patient.

<i>Substance</i>	<i>Potential Negative Effects</i>
Chaparral	Hepatotoxicity
Chondroitin	Anticoagulative properties
Chromium	Hypoglycemia
Dong quai	Anticoagulative properties
Echinacea	Hepatotoxicity
Feverfew	Anticoagulative properties
Garlic	Anticoagulative properties
Ginger	Anticoagulative properties
Ginkgo	Anticoagulative properties
Ginseng	Anticoagulative properties Hypertension

	Hypoglycemia
Goldenseal	Can reduce effect of antihypertensives
Kava	Potentiates the sedative effects of anesthetics Hepatotoxicity
Licorice root	Hypertension Hyperkalemia Hypokalemia Hypernatremia Edema
Ma Huang (ephedra)	Arrhythmias Hypertension
Red yeast rice	Hepatotoxicity
St. John's wort	Prolongation of anesthetic effects Inhibits reuptake of serotonin, dopamine, and noradrenaline
Valerian	Prolongation of anesthetic effects Hepatotoxicity
Vitamin E	Anticoagulative properties

CAM Approaches that May Benefit the Surgical Patient

The two domains in which there is the most research and the most promise with regard to surgical patients are mind–body-based therapies and approaches based in complete systems, specifically oriental medicine and acupuncture.

Oriental Medicine and Acupuncture

A review of the use of acupuncture as the sole source of anesthesia for patients undergoing cesarean delivery in China reviewed 12 years of experience with success rates of 92% to 99%. Blood pressure, heart rate and respiratory rate remained stable throughout the surgery, which is a significant advantage over pharmaceutical anesthesia (76). Although it is unlikely that acupuncture will readily be used as the only source of anesthesia in this country, it does demonstrate the effectiveness of this approach and encourage its consideration as an adjunct. In one randomized controlled trial in patients undergoing upper- and lower-abdominal (gastrointestinal) surgery, acupuncture was given 2.5 cm lateral to the spine

before induction. Postoperatively, patients who received the acupuncture had decreased postoperative pain, nausea and vomiting, analgesic requirement, and sympathoadrenal responses. Supplemental morphine use dropped by 50%, and postoperative nausea was reduced by 30%. Cortisol and epinephrine levels were reduced 30% to 50% during the recovery phase and the first postoperative day (77).

In a sham-controlled trial, the intensity of transcutaneous acupoint electrical stimulation (TAES) was studied in women undergoing lower-abdominal surgery. In patients receiving high-intensity TAES (9–12 mA), there was a 65% decrease in analgesia requirement, decreased duration in patient-controlled anesthesia therapy, and decrease in nausea, vomiting, and pruritus (78).

In Germany, auricular electrically stimulated anesthesia is frequently used. Review of one randomized controlled trial in patients anesthetized with *desflurane* with and without auricular acupuncture revealed significantly reduced anesthetic requirement (the amount of anesthesia required to prevent purposeful movements) (79).

Acupuncture warrants further investigation as an adjunct to anesthesia in gynecologic patients. Even simple adjuncts, such as the use of acupressure bands or electroacupressure bands, are reasonable to support as they are safe and have shown some efficacy in decreasing nausea and vomiting postoperatively.

Mind-body Interventions

Mental preparation for surgery results in psychological, physiologic, and economic benefit. Higher levels of anxiety are associated with a greater risk of complications, depression, increased need for anesthesia, decreased immune function, and a longer time to heal. Many different physiologic aspects are affected, including decreased chemotaxis and phagocytosis and decreased inflammatory factors such as cytokines. One study examining wound healing took healthy dental students and made a standardized scalpel incision in the palate at two times: one right before exams and one during summer vacation. The incisions in these healthy students took 3 days (40%) longer to heal during times of stress versus times of decreased stress (80). The power of the spoken word was explored as long ago as 1964, when a study randomized patients to a preoperative visit characterized by sympathetic, caring, and informative communication versus an interchange characterized by cursory remarks. The patients receiving the sympathetic preoperative visit required one half the pain medicine and had a two- and one-half day decreased hospital stay (81).

A meta-analysis of mind–body interventions and surgery included 191 studies and more than 8,600 patients. **The use of mind–body approaches, including such interventions as hypnosis, imagery, and relaxation, was associated with reduced blood loss, decreased pain, decreased medication use, increased return of bowel function, decreased psychological stress, and decreased hospital stay by 1.5 days.** In a study designed to examine the impact of preoperative instructions, patients undergoing spinal procedures involving fusions or instrumentation (surgeries associated with significant blood loss) were enrolled. All subjects received a 15-minute interaction with a psychologist. The subjects were randomized into one of three groups receiving either direct simple information alone, information plus instruction in muscle relaxation, or information plus instruction in visualizing the blood moving away from the surgical site during surgery. Controlling for the length of surgery and incision length, the estimated blood loss in the first two groups averaged 900 mL and in the third group was 500 mL (82).

In a study of ambulatory surgery patients receiving spinal anesthesia, patients who were randomized to listening to soothing music had decreased sedative requirements both during the surgery and in the perioperative period (83). Patients undergoing cataract surgery were randomized to receive a 5-minute hand massage preoperatively or to the control group. When compared with the control group, the intervention group had significantly decreased levels of anxiety, systolic blood pressure, diastolic blood pressure, heart rate, and epinephrine and norepinephrine (84).

In a study of women undergoing hysterectomy, patients received standardized anesthesia and were randomized to music during surgery, music plus positive suggestions, or the sounds of the operating room. On the day of surgery, both the music group and the music-plus-suggestion groups received significantly less rescue anesthesia. On postoperative day 1, the patients who had received music had more effective analgesia and early mobilization. At the time of discharge, both intervention groups had less fatigue. There was no change in nausea and vomiting, bowel function, or length of stay (85).

In another study with patients undergoing abdominal hysterectomy, patients were randomized to listen intraoperatively to one of four tapes: positive suggestions regarding pain, or nausea and vomiting, or both, or white noise. The positive suggestions had no beneficial effects in reducing nausea and vomiting or the consumption of analgesics or antiemetics (86). In another randomized controlled trial in patients undergoing thyroidectomy under general anesthesia, patients were randomized to listen to taped positive suggestions during surgery versus

a blank tape. The group receiving the suggestions had less nausea and vomiting (47% versus 85%), and less antiemetic treatment (30% versus 68%) (87). In a study exploring the timing of listening to taped suggestions, patients who received the suggestions preoperatively had a 30% decrease in estimated blood loss. Patients receiving the suggestions both pre- and perioperatively had a 26% decrease in blood loss, and in the group listening to the suggestions only intraoperatively, there was a 9% decrease in blood loss. The authors suggest that the preoperative suggestions may be the critical factor (88).

In a retrospective study examining the use of hypnosis plus conscious sedation for plastic surgery, the patients who received hypnosis had better pain and anxiety relief, decreased nausea and vomiting, a significant reduction in *midazolam* and *alfentanil* requirements, and patient satisfaction was significantly increased (89).

Although the studies and interventions in mind–body approaches in the surgical patient are varied, these interventions are low cost and low risk and may offer very real benefits for the patient, as well as a greater sense of empowerment.

Conclusion

As physicians driven by our desire and commitment to provide the best possible care, we have a responsibility to inform our patients of all therapies that can be of benefit, regardless of their system of origin. In practice this is challenging, because not only are there are many unanswered questions in the use of complementary and alternative modalities, there is no established standard of care. Each physician, together with his or her patient, needs to form his or her own opinions regarding the appropriate integration of CAM therapies. Many patients will want conclusive evidence of any therapy before using it. Others, assured of the relative safety of a therapy, may require less conclusive evidence. Illustrating this dilemma, in a systematic review of randomized trials regarding CAM approaches to PMS, the authors concluded that “despite some positive findings, the evidence was not compelling for any of these therapies, with most trials suffering from various methodological limitations. On the basis of current evidence, no complementary or alternative therapy can be recommended as a treatment for premenstrual syndrome (90).” Although this concept certainly is appealing in its simplicity, it may not be in the best interest of patients. We need to be consistent in our requirement of evidence, using the same levels of evidence for incorporating interventions from CAM as from conventional approaches. As with many clinical decisions we are forced to make with incomplete data, many factors must be considered. The potential risks and benefits must

be weighed carefully, and *primum non nocere* must certainly be our guide.

In many regards, we are in the most challenging time as it relates to integrating appropriate CAM approaches into the practice of gynecology. In the future, as more research is done and as medical schools and residency programs incorporate education about these approaches, the gap between our patients' desires and our standard practices will continue to lessen as appropriate therapies are seamlessly incorporated and ineffective and fraudulent ones are discarded.

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14

Benign Diseases of the Female Reproductive Tract

Paula J. Hillard Adams



- **The causes of abnormal bleeding vary by age, with anovulatory bleeding most likely in adolescents and perimenopausal women.**
- **Pelvic masses in adolescents are most commonly functional or benign**

neoplastic ovarian masses, whereas the risks of malignant ovarian tumors increases with age.

- **Although pelvic ultrasonography is an excellent technique for imaging pelvic masses, and ultrasonographic characteristics may suggest reassuring characteristics of an ovarian mass, the possibility of malignancy must be kept in mind.**
- **Vulvovaginal symptoms of any sort in a young child should prompt the consideration of possible sexual abuse.**
- **Most uterine leiomyomas are asymptomatic, although bleeding, pressure symptoms, or pain may necessitate medical or surgical management.**

Benign gynecologic conditions can present with a variety of signs and symptoms that vary by age. In this chapter, the most likely causes of specific signs and symptoms, as well as diagnosis and management, are described for each age group: prepubertal, adolescent, reproductive age, and postmenopausal women. **The common gynecologic problems include those that cause pain, bleeding, pelvic masses (which may be symptomatic or asymptomatic), as well as vulvar and vaginal symptoms.** Benign conditions of the female genital tract include anatomic lesions of the uterine corpus and cervix, ovaries, fallopian tubes, vagina, and vulva. A classification of benign lesions of the vulva, vagina, and cervix appears in Table 14.1. Leiomyoma, polyps, and hyperplasia are the most common benign conditions of the uterus in adult women. Benign tumors of the ovaries are listed in Table 14.2. Malignant diseases are presented in Chapters 33,34,35,36,37, through 38.

Table 14.1 Classification of Benign Conditions of the Vulva, Vagina, and Cervix

Vulva**Skin conditions****Pigmented lesions****Tumors and cysts****Ulcers****Nonneoplastic epithelial disorders****Vagina****Embryonic origin**

Mesonephric, paramesonephric, and urogenital sinus cysts

Adenosis (related to diethylstilbestrol)

Vaginal septa or duplications

Disorders of pelvic support**Anterior vaginal prolapse**

Cystourethrocele

Cystocele

Apical vaginal prolapse

Uterovaginal

Vaginal vault

Posterior vaginal prolapse

Enterocoele

Rectocele

Other

Condyloma

Urethral diverticula

Fibroepithelial polyp

Vaginal endometriosis

Cervix**Infectious**

Condyloma

Herpes simplex virus ulceration

Chlamydial cervicitis

Other cervicitis

Other

Endocervical polyps
Nabothian cysts
Columnar epithelium eversion

Table 14.2 Benign Ovarian Tumors
<i>Functional</i>
Follicular
Corpus luteum
Theca lutein
<i>Inflammatory</i>
Tubo-ovarian abscess or complex
<i>Neoplastic</i>
Germ cell
Benign cystic teratoma
Other and mixed
<i>Epithelial</i>
Serous cystadenoma
Mucinous cystadenoma
Fibroma
Cystadenofibroma
Brenner tumor
Mixed tumor
<i>Other</i>
Endometrioma

Prepubertal Age Group

Bleeding

Before menarche, occurring no younger than age 9 years, any bleeding requires evaluation. To appropriately evaluate a young girl with vaginal bleeding, a practitioner should understand the events of puberty (1,2,3). The hormonal changes that control

An understanding of the normal sequence and timing of these events is critical to an appropriate assessment of a girl at the onset of bleeding (see Chapter 26). Menarche typically occurs when an adolescent has reached Tanner stage 3–4 of breast development (Fig. 14.1).

Differential Diagnosis

Slight vaginal bleeding can occur within the first few days of life because of withdrawal from exposure to high levels of maternal estrogen. New mothers of female infants should be informed of this possibility to preclude unnecessary anxiety. After the neonatal period, a number of causes of bleeding should be considered in this age group (Table 14.3). Menses rarely occurs before breast budding (4,5). Vaginal bleeding in the absence of secondary sexual characteristics should be evaluated carefully.

The causes of bleeding in this age group range from the medically mundane to malignancies that may be life threatening. The source of the bleeding is sometimes difficult to identify, and parents who observe blood in a child's diapers or panties may be unsure of the source. Pediatricians usually will look for urinary causes of bleeding, and gastrointestinal factors should also be considered. The possibility of abuse should always be considered in girls with any vulvovaginal symptoms, particularly if bleeding is present. Failure to diagnose sexual abuse may leave a child in significant danger.

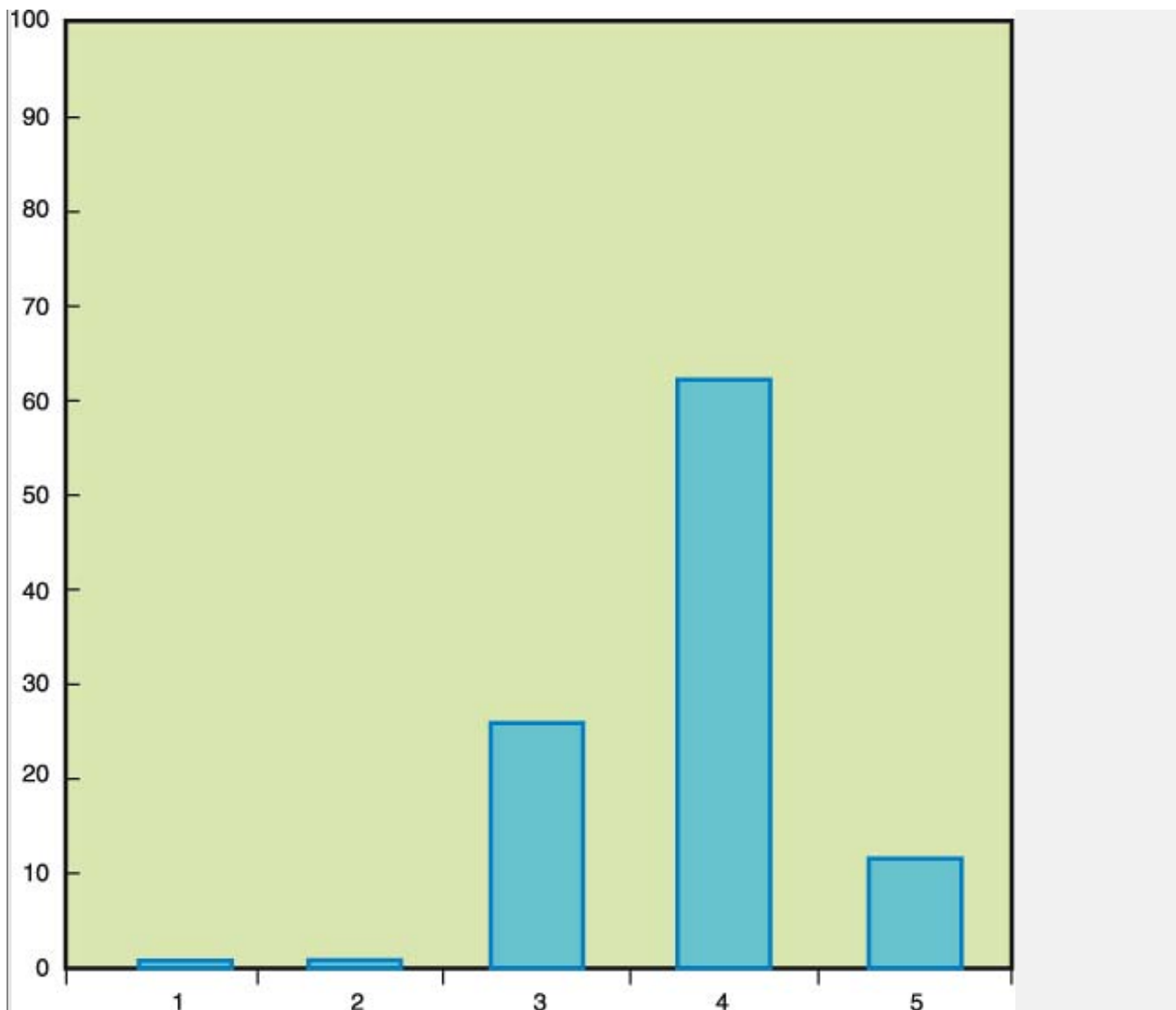


Figure 14.1 Tanner breast stage at menarche. Data adapted from Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; 44: 291–303.

Vulvar Lesions

Vulvar irritation can lead to pruritus with excoriation, maceration of the vulvar skin, or fissures that can bleed. Other visible external causes of bleeding in this age group include urethral prolapse, condylomas, lichen sclerosus, or molluscum contagiosum. **Urethral prolapse**

can present acutely with a tender mass that may be friable or bleed slightly; it is most common in African-American girls and may be confused with a vaginal mass (Fig. 14.2). The classic presentation is a mass symmetrically surrounding the urethra. This condition can be managed medically with the topical application of estrogens (6). The presence of condyloma should prompt questioning about abuse, although it has been suggested that **condyloma that appears during the first 2 to 3 years of life may have been acquired perinatally from maternal infection with human papillomavirus** (7,8) (Fig. 14.3). Excoriation and hemorrhage into the skin can cause external bleeding in the presence of prepubertal lichen sclerosus; this finding may mistakenly be identified as abuse, although the conditions are not mutually exclusive (9) (Fig. 14.4). **Although most gynecologists recognize the appearance of lichen sclerosus in postmenopausal women, the condition also occurs in prepubertal girls and may not be recognized by clinicians who are familiar with this condition.** As with adults, the cause of lichen sclerosus remains uncertain; a familial incidence has been identified (10).

Foreign Body

A foreign body in the vagina is a common cause of vaginal discharge, which may appear purulent or bloody. Young children explore all orifices and may place all varieties of small objects inside their vaginas (Fig. 14.5). An object, such as a small plastic toy, can sometimes be palpated on rectal examination. The most common foreign bodies found in the vagina are small pieces of toilet paper (11). One study suggests that the presence of vaginal foreign bodies may be a marker for sexual abuse; although this is by no means always the case, the possibility of abuse should be considered (12).

Table 14.3 Causes of Vaginal Bleeding in Prepubertal Girls

Vulvar and external

Vulvitis with excoriation

Trauma (e.g., accidental injury [straddle injury] or sexual abuse)

Lichen sclerosus

Condylomas

Molluscum contagiosum

Urethral prolapse

Vaginal

Vaginitis

Vaginal foreign body
Trauma (abuse, penetration)
Vaginal tumor
<i>Uterine</i>
Precocious puberty
<i>Ovarian tumor</i>
Granulosa cell tumor
Germ cell tumor
<i>Exogenous estrogens</i>
Topical
Enteral



Figure 14.2 Urethral prolapse.



Figure 14.3 Periurethral condyloma.



Figure 14.4 Prepubertal lichen sclerosus.

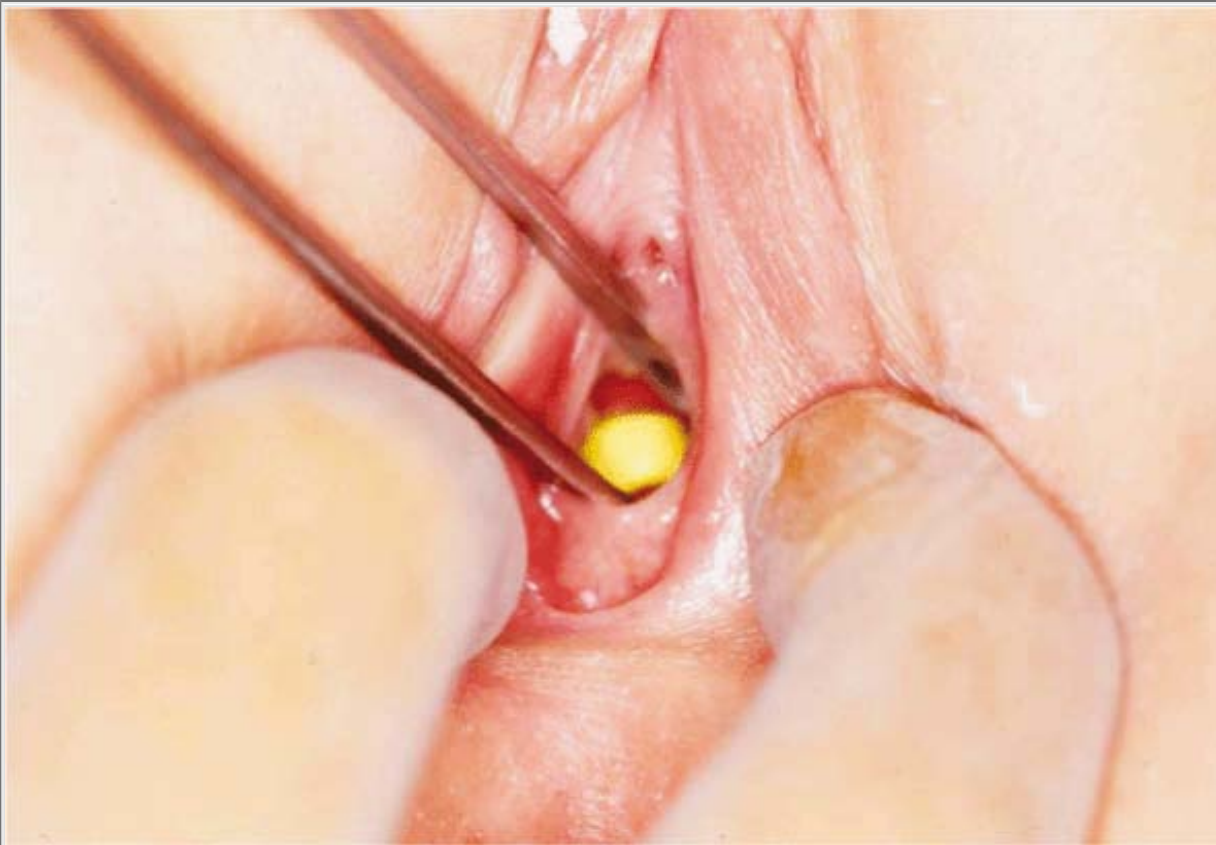


Figure 14.5 Foreign body (plastic toy) in the vagina of an 8-year-old girl.

Precocious Puberty

Vaginal bleeding in the absence of other secondary sexual characteristics may result from precocious puberty (see Chapter 26), although the onset of breast budding or pubic hair growth are more likely to occur before vaginal bleeding. A large observational study suggests that the onset of pubertal changes—breast budding and pubic hair—may occur earlier than had originally been thought (2). Previously, evaluation for precocious puberty was recommended for girls with pubertal development younger than age 8 years. New guidelines from the Pediatric Endocrine Society propose evaluation of white girls younger than age 7 years and African-American girls younger than age 6 years who have either breast development or pubic hair (13).

Trauma

Trauma can be a cause of genital bleeding. **A careful history should be obtained from one or both parents or caretakers and the child herself, because trauma caused by sexual abuse often is not recognized.** Physical findings that are inconsistent with the description of the alleged accident should prompt consideration of abuse and appropriate consultation or referral to an experienced social worker or sexual abuse team. **All states impose a mandatory legal obligation to report suspected child physical abuse;** most states specifically require reporting child sexual abuse as well, but even in those that do not, the laws are broad enough to encompass sexual abuse implicitly (14). Notification is required even with the suspicion of sexual abuse. In general, straddle injuries affect the anterior and lateral vulvar area (Fig. 14.6), whereas penetrating injuries with lesions of the fourchette or lesions that extend through the hymenal ring are less likely to occur as a result of accidental trauma (15,16).

Abuse

The medical evaluation of suspected child sexual abuse is best managed by individuals who have experience in assessing the physical findings, laboratory results, and the children's statements and behaviors. Genital findings have been described as follows (17):

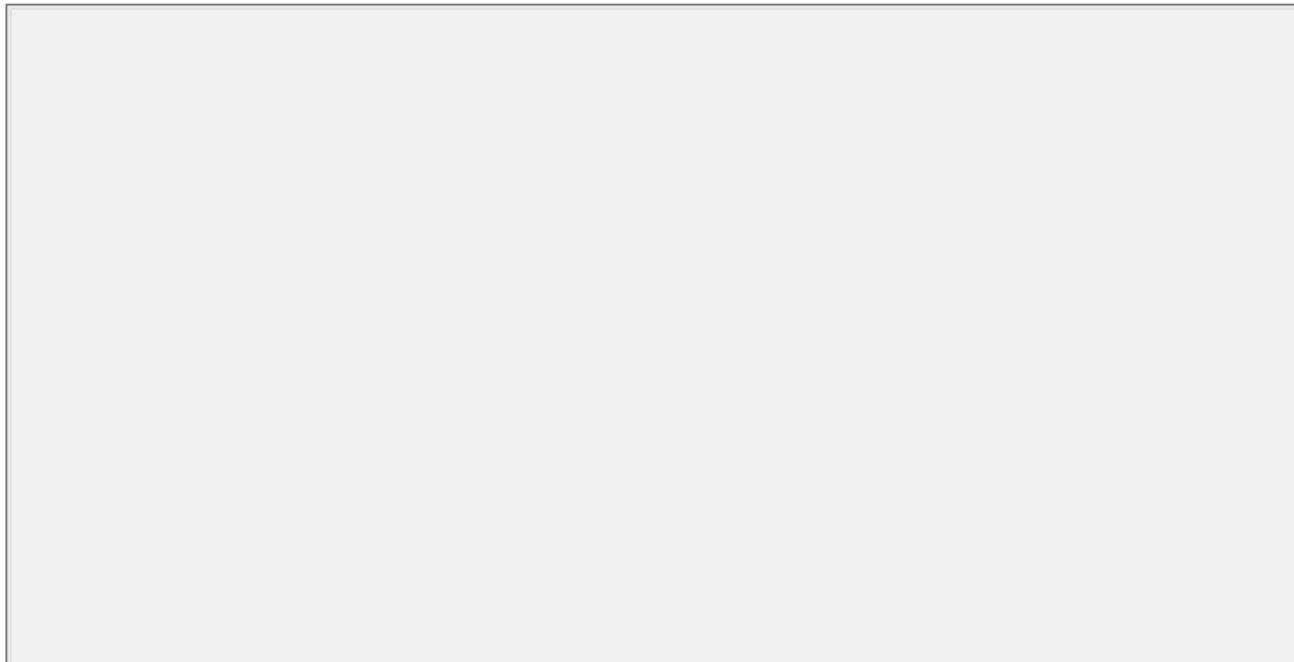




Figure 14.6 Straddle injury—vulvar hematoma in a 13-year-old girl.

- Normal or unrelated to abuse
- Nonspecific for abuse
- Concerning for abuse

Clear evidence of blunt force or penetrating trauma.

The overall classification of the likelihood for abuse can be categorized as follows (17):

- No evidence of abuse
- Possible abuse
- Probable abuse
- Definitive evidence of abuse or penetrating trauma.

Most cases of child sexual abuse do not come to light with an acute injury and instead are associated with normal or nonspecific genital findings (18,19,20). Forms of abuse such as fondling or digital penetration may not result in visible genital lesions.

Other Causes

Other serious but rare causes of vaginal bleeding include vaginal tumors. The most common tumor in the prepubertal age group is a rhabdomyosarcoma

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(sarcoma botryoides), which is associated with bleeding and a grapelike clustered mass (see Chapter 34). Other forms of vaginal tumor are also rare but should be ruled out with a thorough examination under anesthesia if no other obvious source of bleeding is found externally.

Hormonally active ovarian tumors can cause endometrial proliferation and bleeding. Likewise, exogenously administered estrogens can result in bleeding. Rarely, bleeding can result from the prolonged use of topical estrogens prescribed as therapy for vulvovaginitis or labial adhesions or from accidental ingestion of prescription estrogens.

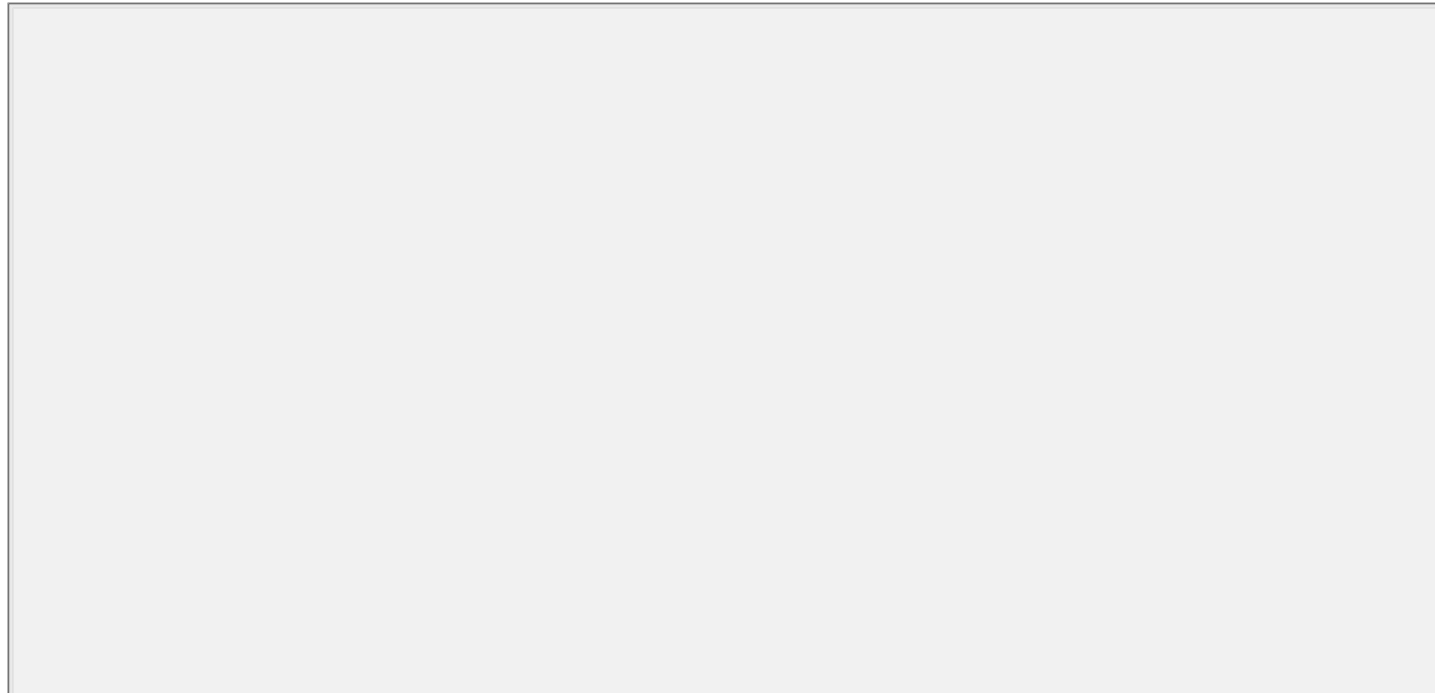
Diagnosis

Examination

A careful examination is indicated when a child has genital symptoms. The technique of examining the prepubertal child is described in Chapter 1. **If no obvious cause of bleeding is visible externally or within the distal vagina, an examination can be performed using anesthesia and an endoscope to completely visualize the vagina and cervix. This examination is best performed by a clinician with experience in pediatric and adolescent gynecology.**

Imaging

If an ovarian or vaginal mass is suspected, a pelvic ultrasonographic examination can provide useful information. The appearance of the ovaries (normal prepubertal size and volume, follicular development, cystic, or solid) can be noted, as well as the size and configuration of the uterus. **The prepubertal uterus has a distinctive appearance, with equal proportions of cervix and fundus and a size of approximately 2 to 3.5 cm in length and 0.5 to 1 cm in width** (Fig. 14.7). The uterine fundus enlarges with estrogen stimulation, resulting in the postmenarchal appearance in which the uterine fundus is larger than the cervix (21). An ultrasonographic examination should be the first imaging study performed; more sophisticated imaging techniques, such as magnetic resonance imaging (MRI) or computed tomography (CT) scanning, add unnecessary expense and are rarely indicated as initial diagnostic modalities.



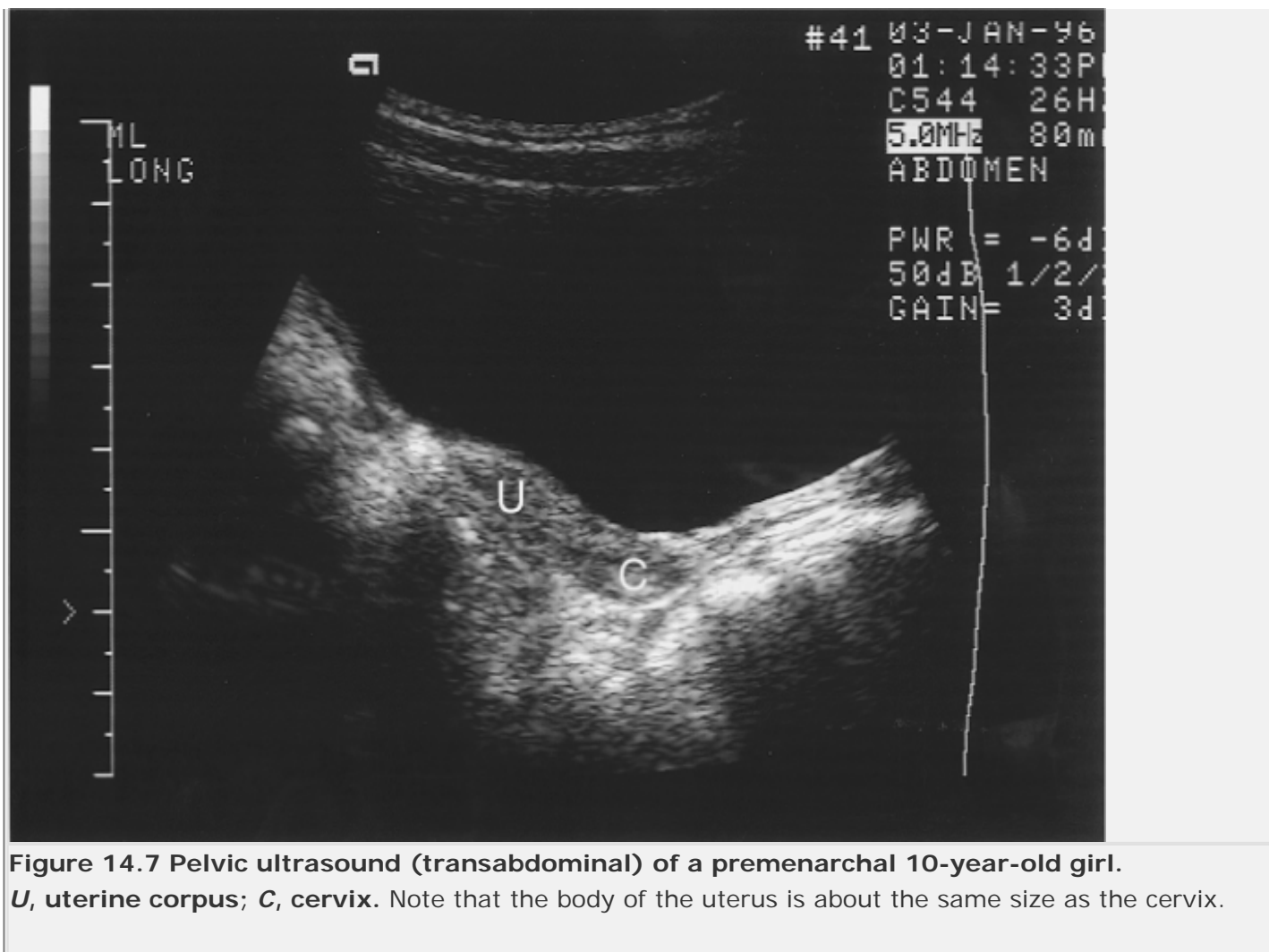


Figure 14.7 Pelvic ultrasound (transabdominal) of a premenarchal 10-year-old girl.
U, uterine corpus; C, cervix. Note that the body of the uterus is about the same size as the cervix.

Management

The management of bleeding in the prepubertal-age girls is directed toward the cause of bleeding. If bloody discharge believed to be due to nonspecific vulvovaginitis persists despite therapy, further evaluation may be necessary to rule out the presence of a foreign body. Skin lesions (chronic irritation) and lichen sclerosus may be difficult to manage but can be treated with a course of topical steroids; lichen sclerosus often requires the use of high-potency topical steroids and ongoing maintenance therapy. **Vaginal and ovarian tumors should be managed in consultation with a gynecologic oncologist.**

Pelvic Masses

Presentation

The probable causes of a pelvic mass found on physical examination or through radiologic studies are vastly different in prepubertal children than they are in adolescents or postmenopausal women (Table 14.4). A pelvic mass may be gynecologic in origin, or it may arise from the urinary tract or bowel. The gynecologic causes of a pelvic mass may be uterine, adnexal, or more specifically ovarian. Because of the small pelvic capacity of a prepubertal child, a pelvic mass very quickly becomes abdominal in location as it enlarges and may be palpable on examination. Ovarian masses in this age group may be asymptomatic, associated with chronic pressure-related bowel or bladder symptoms, or may present with acute pain caused by rupture or torsion. Abdominal or pelvic pain is one of the most frequent initial symptoms. The diagnosis of ovarian masses in prepubertal girls is difficult because the condition is rare in this age group and, consequently, there is a low index of suspicion. Many symptoms are nonspecific, and acute symptoms are more likely to be attributed to more common entities such as appendicitis. **Abdominal palpation and bimanual rectoabdominal examination are important in any child who has nonspecific abdominal or pelvic symptoms.** An ovarian mass that is abdominal in location can be confused with other abdominal masses occurring in children, such as Wilms' tumor or neuroblastoma. Acute pain is often associated with torsion. The ovarian ligament becomes elongated as a result of the abdominal location of these tumors, thus creating a predisposition to torsion.

Table 14.4 Causes of Bleeding and Pelvic Mass by Approximate Frequency and Age Group

<i>Causes of bleeding by approximate frequency and age group</i>					
<i>Infancy</i>	<i>Prepubertal</i>	<i>Adolescent</i>	<i>Reproductive</i>	<i>Perimenopausal</i>	<i>Postmenopausal</i>
	Vulvovaginitis	Anovulation	Exogenous hormone use	Anovulation	Exogenous hormone use
	Vaginal foreign body	Exogenous hormone use	Pregnancy	Fibroids	Endometrial lesions, including cancer
	Precocious puberty	Pregnancy	Anovulation	Cervical and endometrial polyps	Atrophic vaginitis
	Tumor	Coagulopathy	Fibroids	Thyroid dysfunction	Other tumor—vulvar, vaginal, cervical

				Cervical and endometrial polyps	
				Thyroid dysfunction	
<i>Causes of pelvic mass by approximate frequency and age group</i>					
<i>Infancy</i>	<i>Prepubertal</i>	<i>Adolescent</i>	<i>Reproductive</i>	<i>Perimenopausal</i>	<i>Postmenopausal</i>
Functional cyst	Functional cyst	Functional cyst	Functional cyst	Fibroids	Ovarian tumor (malignant or benign)
Germ cell tumor	Germ cell tumor	Pregnancy	Pregnancy	Epithelial ovarian tumor	Functional cyst
		Dermoid/other germ cell tumors	Uterine fibroids	Functional cyst	Bowel, malignant tumor or inflammatory
		Obstructing vaginal or uterine anomalies	Epithelial ovarian tumor		Metastases
		Epithelial ovarian tumor			

Diagnosis

Ultrasonography has become a valuable tool for diagnosing ovarian masses. The characteristics of a pelvic mass can be determined. Whereas both unilocular and multilocular cysts frequently resolve with observation, the finding of a solid component mandates surgical assessment because of the high risk of a germ cell tumor (22). Additional imaging studies, such as CT scanning, MRI, or Doppler flow studies, may be helpful in establishing the diagnosis (23).

Differential Diagnosis

Fewer than 2% of ovarian malignancies occur in children and adolescents (24).

Ovarian tumors account for approximately 1% of all malignant tumors in these age groups. Germ cell tumors make up one half to two thirds of ovarian neoplasms in individuals younger than 20 years of age. A review of studies conducted from 1940

until 1975 concluded that 35% of all ovarian neoplasms occurring during childhood and adolescence were malignant (25). **In girls younger than 9 years of age, approximately 80%**

of the ovarian neoplasms were found to be malignant (26,27). Germ cell tumors account

for approximately 50% of ovarian neoplasms in children and adolescents compared with 20% of these tumors in adults (25). Epithelial neoplasms are rare in the prepubertal age group; thus, data usually are reported from referral centers. However, some reports include only neoplastic masses, whereas others include nonneoplastic masses; some series combine data from prepubertal and adolescent girls. However, one community survey of ovarian masses revealed that the frequency of malignancy was much lower than previously reported; **of all ovarian masses confirmed surgically in childhood and adolescence, only 6% of patients with ovarian enlargement had malignant neoplasms, and only 10% of neoplasms were malignant** (28). Surgical decision making clearly influences the statistics on incidence; the surgical excision of functional masses that would resolve in time inflates the percentage of benign masses. In one series, nonneoplastic masses in young women and girls younger than 20 years of age constituted two thirds of the total (29). Even in girls younger than 10 years of age, 60% of the masses were nonneoplastic, and two thirds of the neoplastic masses were benign. Functional, follicular cysts can occur in fetuses, newborns, and prepubertal children (30). Rarely, they may be associated with sexual precocity.

Management

A plan for the management of pelvic masses in prepubertal age girls is shown in Figure 14.8. **Unilocular cysts are virtually always benign, even in this age group, and will regress in 3 to 6 months; thus, they do not require surgical management with oophorectomy or oophorocystectomy.** Close observation is recommended, although there is a risk of ovarian torsion that must be discussed with the child's parents (31). Recurrence rates after cyst aspiration (either ultrasonographically guided or with laparoscopy) may be as high as 50%. Attention should be directed to long-term effects on endocrine function as well as future fertility; preservation of ovarian tissue is a priority for patients with benign tumors. **Premature surgical therapy for a functional ovarian mass can result in ovarian and tubal adhesions that can adversely affect future fertility.** Solid masses, those larger than approximately 8 cm, and enlarging masses require surgical intervention.

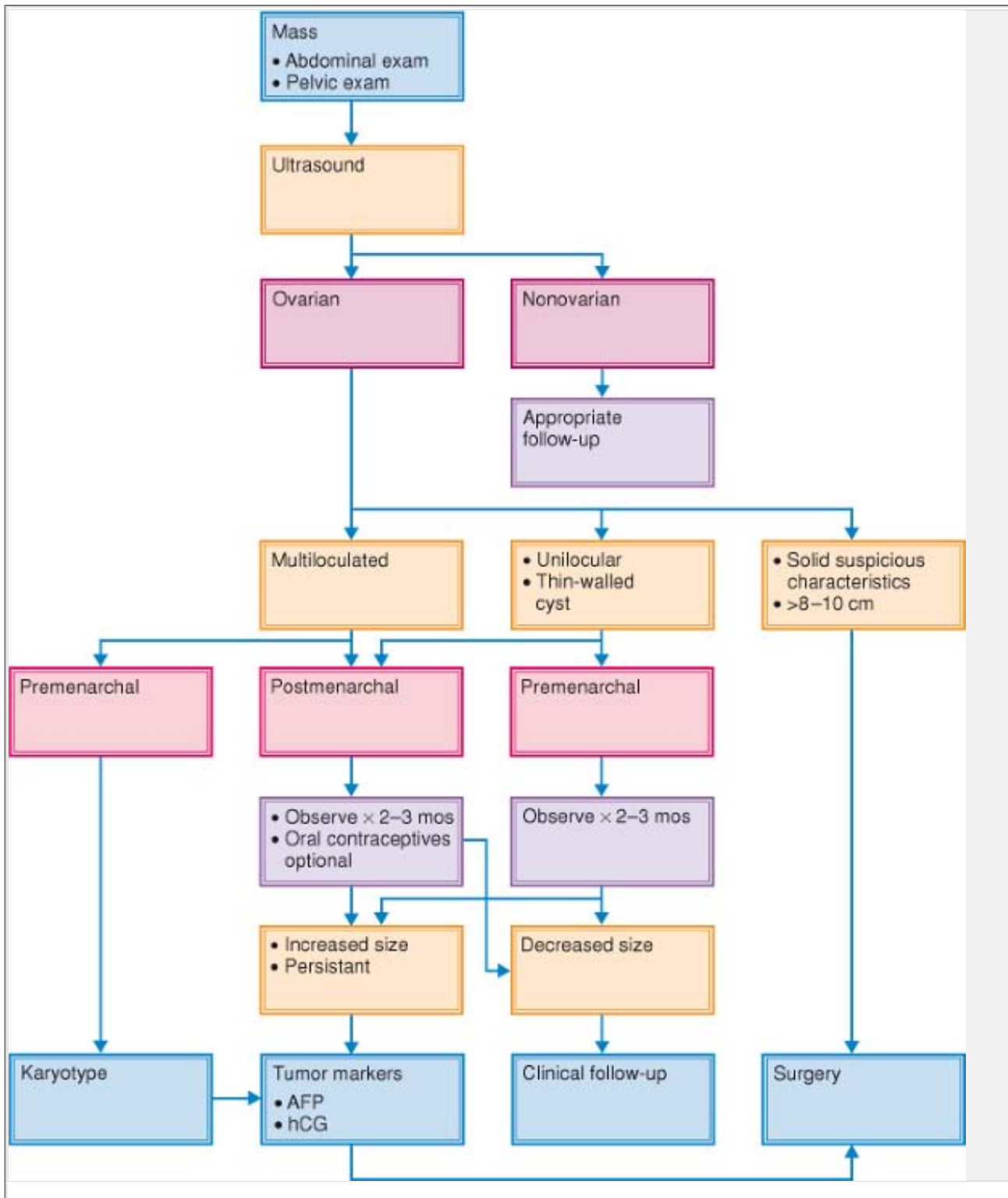


Figure 14.8 Management of pelvic masses in premenarchal and adolescent girls.

Vulvar Conditions

Neonatal Vulvar Conditions

Various developmental and congenital vulvovaginal abnormalities occur in the neonatal age group. Whereas an extensive discussion of these abnormalities is beyond the scope of this text, obstetrician-gynecologists will recognize that they must be prepared to deal with

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the parents and family when an infant is born with ambiguous genitalia. The etiology of these problems, as well as intersex disorders that may be discovered in an older child, can be complex. Chromosomal abnormalities, enzyme deficiencies (including 17- or 21-hydroxylase deficiency as causes of congenital adrenal hyperplasia), or prenatal masculinization of a female fetus resulting from maternal androgen-secreting ovarian tumors or, rarely, drug exposure can all result in genital abnormalities that are noted at birth. These abnormalities are described in Chapter 26.

Ambiguous genitalia represent a social and potential medical urgency that is best handled by a team of specialists, which may include urologists, neonatologists, endocrinologists, and pediatric gynecologists. The first questions parents ask after a baby is born include, "Is it a boy or a girl?" In the case of ambiguous genitalia, the parents should be informed that the baby's genitals are not fully developed and, therefore, a simple examination of the external genitalia cannot determine the actual sex. The parents should be told that data will be collected but that it may take several days or longer to determine the baby's intended sex. In some situations, it may be best to state simply that the baby has some serious medical complications. The issues of sex assignment and timing of surgical therapy are controversial and should be managed by clinicians with extensive experience in this area (32,33,34).

Other genital abnormalities may be noted at birth, although few obstetricians or pediatricians carefully examine the external genitalia of female neonates. It has been argued that **careful inspection of the external genitalia of all female infants should be performed, with gentle probing of the introitus and anus to determine the patency of the hymen or a possible imperforate anus.** If patency is in doubt, a rectal thermometer may be used to gently test the patency. It has been suggested that this examination should be performed on all female infants in the delivery room (35,36). Various types of

hymenal configurations in the newborn have been described, ranging from imperforate to microperforate, to cribriform, to hymenal bands, and to hymens with central anterior, posterior, or eccentric orifices (37). An examination during the neonatal period would prevent the discovery of an imperforate hymen or vaginal septum after a young woman experiences periodic pelvic and abdominal pain with the development of a large hematometra or hematocolpos (38).

Congenital vulvar tumors may include strawberry hemangiomas, which are relatively superficial vascular lesions, and large cavernous hemangiomas. Treatment is controversial; many lesions will spontaneously regress. Some clinicians have advocated cryotherapy, argon laser therapy, or sclerosing solutions (39).

Childhood Vulvar Conditions

Vulvar and vaginal symptoms, such as burning, dysuria, itching, or a rash, are a common initial symptom reported to gynecologists among children. It may be difficult for a young child to describe vulvar sensations. Parents may notice the child crying during urination, scratching herself repeatedly, or complaining of vague symptoms. Often, the child's pediatrician will have evaluated the child for urinary tract infection. Evaluation for pinworms is also warranted, because pinworms can cause severe itching in the vulvar as well as perianal area. **Vulvovaginitis is the most common gynecologic problem of childhood.** Prepubertally, the vulva, vestibule, and vagina are anatomically and histologically vulnerable to infection, with the bacteria typically present in the perianal area. The physical proximity of the vagina and vestibule to the anus can result in overgrowth of bacteria that can cause primary vulvitis and secondary vaginitis. Yeast infections are uncommon in prepubertal children who are toilet trained (40).

The clinician should be familiar with normal prepubertal genital anatomy and hymenal configuration (41,42). **The unestrogenized vulvar vestibule is mildly erythematous and can be confused with infection. In addition, smegma around and beneath the prepuce**

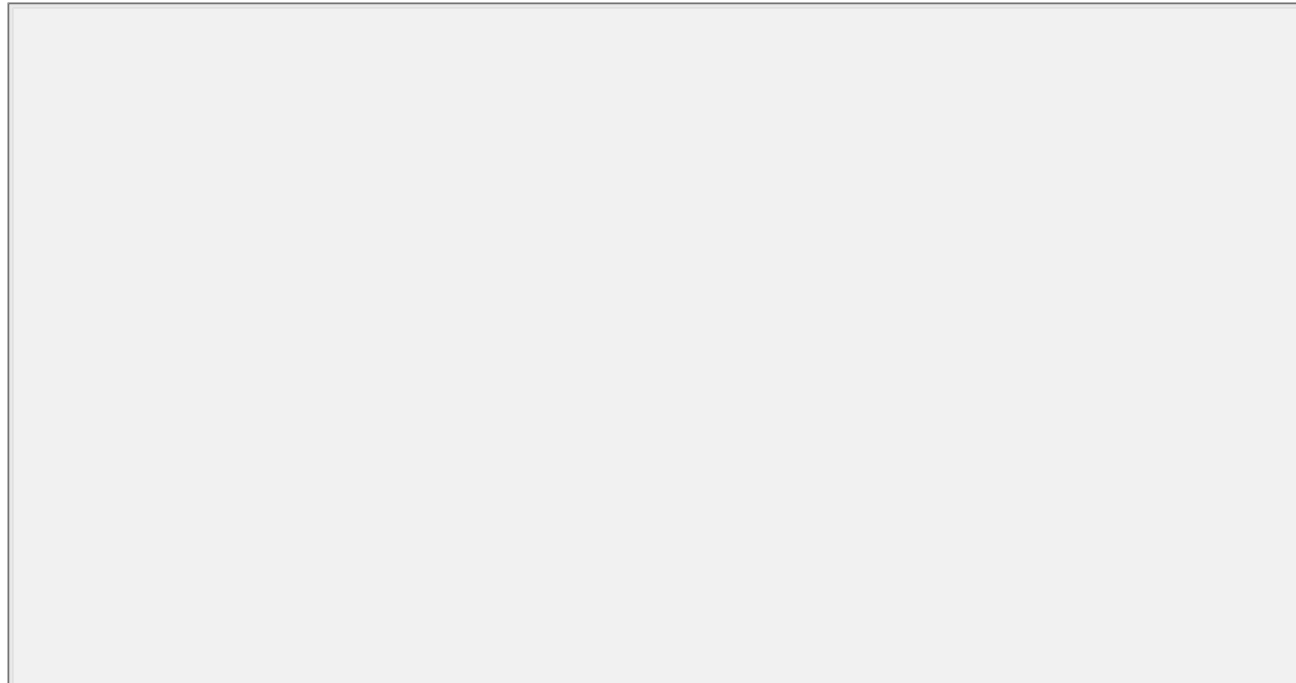
may resemble patches of candida vulvitis. In prepubertal girls, the vulvar area is quite susceptible to chemical irritants.

Chronic skin conditions such as lichen sclerosus, psoriasis, seborrheic dermatitis, and atopic vulvitis may occur in children (43). Lichen sclerosus, the cause of which is not well established, has a characteristic "cigarette paper" appearance in a keyhole distribution (around the vulva and anus) (Fig. 14.4). Lichen sclerosus should be treated in pediatric patients as it is in adults; there is some evidence that the condition may regress as the child progresses through adrenarche and menarche. The use of ultrapotent steroids topically has been successful in

children as well as adults (44).

Labial agglutination or adhesions may occur as a result of chronic vulvar inflammation from any cause (Fig. 14.9A). The treatment of labial adhesions consists of a brief course (2 to 6 weeks) of externally applied estrogen cream. The area of agglutination (adhesion) will become thin as a result, and separation can usually be performed in the office with the use of a topical anesthetic (e.g., lidocaine jelly) (Fig. 14.9B). Manual separation in the office without pretreatment with topical estrogen and without anesthesia is discouraged, as this practice may be so traumatic to the child that she will not allow subsequent examination. In the absence of a previously traumatic examination or previous surgical separation with recurrence, surgical separation frequently is not required (45). Treatment with a topical emollient (such as petrolatum) is indicated to prevent recurrent adhesions. Urethral prolapse may cause acute pain or bleeding, or the presence of a mass may be noted (Fig. 14.2).

Vulvovaginal symptoms of any sort in a young child should prompt the consideration of possible sexual abuse. Sexually transmitted infections may occur in prepubertal children (46). Although vulvar condyloma presenting before age 2 to 3 years can be transmitted during vaginal delivery from the mother or from warts on caretakers' hands, the possibility of abuse should be considered in all children with genital warts (47). Sensitive but direct questioning of the parent or caretaker and the child should be a part of the evaluation; if sexual abuse is suspected, the incident must be reported to the appropriate social services agency.



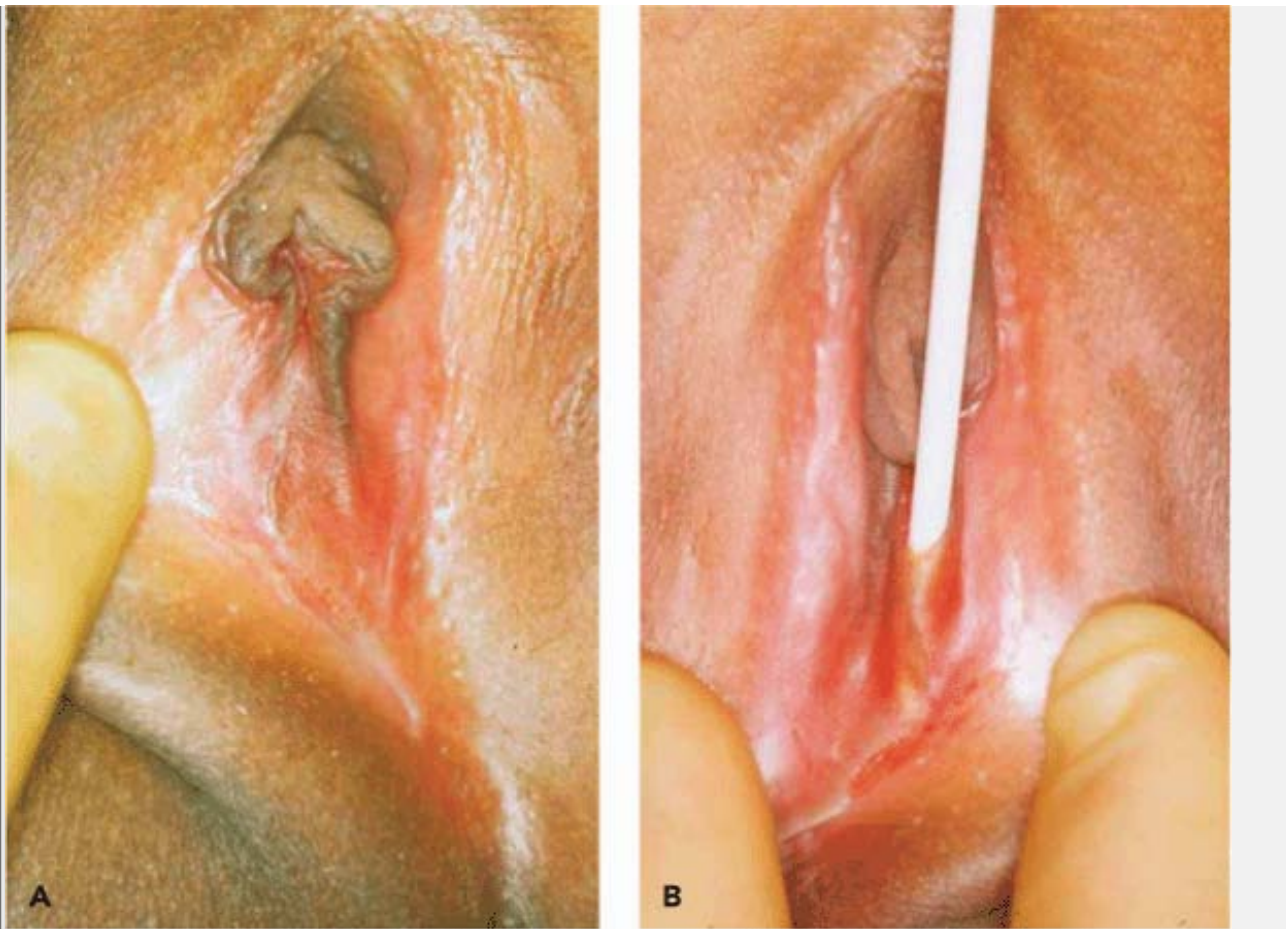


Figure 14.9 A: Labial adhesions. B: Cotton-tipped applicator placed inside the labial agglutination shown in (A).



Figure 14.10 Vulvar ulcer in prepubertal girl.

Nonsexually transmitted vulvar ulcers can occur in peripubertal and adolescent girls, often in association with systemic symptoms suggestive of a viral illness (48) (Fig. 14.10). Herpes simplex virus, syphilis, and Behçet's disease can cause vulvar ulcers, but they also may occur as a form of genital aphthosis.

Vaginal Conditions

Vaginal Discharge

The symptom of vaginal discharge in the prepubertal age group is almost always caused by inflammation and irritation. In prepubertal girls, the primary site typically is the vulva, with vaginitis following secondarily, whereas in adolescents and adults, vaginitis typically is

the primary finding with vulvitis occurring secondarily. **Sexual abuse should always be considered in prepubertal children with vaginal discharge or a foreign body** (12). Although the routine use of cultures to detect sexually transmitted diseases (STDs) in girls with a history of sexual abuse has been questioned, vaginal culture for gonorrhea and chlamydia should be performed in girls who have vaginal discharge (49). In prepubertal girls, vulvovaginitis is usually caused by multiple organisms that are present in the perineal area, although a single organism such as *Streptococcus*, or even rarely *Shigella*, may be causative (50). When the cause is related to poor perineal hygiene, cultures often reveal a mixture of bacterial organisms. In this situation, the typical history is intermittent symptoms of irritation, itching, discharge, and odor over many months to years. Treatment should be initiated with a focus on hygiene and cleansing measures (51). A short-term (less than 4 weeks) course of treatment with topical estrogens and broad-spectrum antibiotics may be necessary. The problem is frequently recurrent. In girls who have a relatively acute onset of vaginal

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discharge and vulvovaginal symptoms, a single bacterial organism is more likely to be the cause of their symptoms.

Pokorny and Stormer has described a technique for obtaining vaginal cultures and for performing vaginal irrigation (52). A catheter within a catheter can be fashioned using the tubing from an intravenous butterfly setup within a sterile urethral catheter. Nonbacteriostatic saline (1–3 mL) can be injected, aspirated, and sent for culture. Cultures taken in this manner are almost always better tolerated than cultures obtained using a cotton-tipped applicator. A larger quantity of saline can then be used to irrigate the vagina while the catheter is still within the vagina. Small foreign bodies can often be flushed from the vagina in this manner. The most common foreign body is a small piece of toilet paper, although children will place other objects (toys, beans, coins) within their vaginas (Fig. 14.5). **A persistent vaginal discharge after treatment, or a discharge that is bloody or brown in color without other obvious external lesions, should prompt vaginal irrigation or vaginoscopy to rule out a foreign body** (53).

Adolescent Age Group

The adolescent's experience and expression of illness and pain should be viewed within the context of her life experiences. Most adolescents have had limited life experiences with problems such as pain, discomfort, or bleeding. An adolescent may state that she is experiencing the "worst pain of her life" and yet may appear to be reasonably comfortable. She may well be stating the truth about this experience, which the clinician must still interpret differently from

the symptoms of an adult woman who, for instance, may be in active labor. It should be remembered that an individual's responses to illness and pain are to some extent learned behaviors.

Abnormal Bleeding

Normal Menses

To assess vaginal bleeding during adolescence, it is necessary to have an understanding of the range of normal menstrual cycles (see Chapter 7). **During the first 2 years after menarche, most cycles are anovulatory. Despite this, they are somewhat regular, within a range of approximately 21 to 42 days (54,55,56,57), in contrast to adult women, whose cycles typically range between 21 and 35 days.** In more than one fourth of girls, a pattern of plus or minus 10 days and a cycle length of 21 to approximately 42 days are established within the first three cycles; in one half of girls, the pattern is established by the seventh cycle; and in two thirds of girls, such a pattern is established within 2 years of menarche (56).

The mean duration of menses is 4.7 days; 89% of cycles last 7 days. The average blood loss per cycle is 35 mL (58), and the major component of menstrual discharge is endometrial tissue. Recurrent bleeding in excess of 80 mL/cycle results in anemia.

Quantitative information about the volume of menstrual blood loss is of little clinical use. The common clinical practice of asking how many pads or tampons are soaked on a heavy day or per cycle can give a rough approximation of blood loss (3 to 5 pads per day is typical). Individual variations in fastidiousness, lack of familiarity with the volume of blood loss other than one's own, and errors in estimation or recollection result in inaccuracies in estimations of menstrual volume. One study found that one third of individuals who estimated their cycles to be moderate or light had bleeding in excess of 80 mL/cycle, whereas nearly one half of those who described the bleeding as heavy had flow less than 80 mL/cycle (59). In addition, the amount of menstrual blood

contained in each tampon or pad may vary both within brands as well as from one brand to another (60).

The transition from anovulatory to ovulatory cycles takes place during the first several years after menarche. It results from the so-called *maturation of the hypothalamic-pituitary-ovarian axis*, characterized by positive feedback mechanisms in which

a rising estrogen level triggers a surge of luteinizing hormone and ovulation. **Most adolescents have ovulatory cycles by the end of their second year of menstruation, although most cycles (even anovulatory ones) remain within a rather narrow range of approximately 21 to 42 days.**

Differential Diagnosis

Cycles that are longer than 42 days, cycles that are shorter than 21 days, and bleeding that lasts more than 7 days should be considered abnormal, particularly after the first 2 years from the onset of menarche. The variability in cycle length is greater during adolescence than adulthood; thus, greater irregularity is acceptable if neither significant anemia nor hemorrhage is present. However, consideration should be given to an evaluation of possible causes of abnormal menses (particularly underlying causes of anovulation such as androgen excess syndromes or causes of oligomenorrhea such as eating disorders) for girls whose cycles are consistently outside normal ranges (61) or whose cycles were previously regular and become irregular (57). Conditions that are associated with abnormal bleeding are listed in Table 14.5 and more fully discussed in Chapter 26,27, and 28.

Anovulation

Anovulatory bleeding can be too frequent, prolonged, or heavy, particularly after a long interval of amenorrhea. The physiology of this phenomenon relates to a failure of the feedback mechanism in which rising estrogen levels result in a decline in follicle-stimulating hormone (FSH) with subsequent decline of estrogen levels. In anovulatory cycles, estrogen secretion continues, resulting in endometrial proliferation with subsequent unstable growth and incomplete shedding. The clinical result is irregular, prolonged, and heavy bleeding.

Studies of adolescent menses show differences in rates of ovulation based on the number of months or years postmenarche. **The younger the age at menarche, the sooner regular ovulation is established.** In one study, the time from menarche until 50% of the cycles were ovulatory was 1 year for girls whose menarche occurred when they were younger than 12 years of age, 3 years for girls whose menarche occurred between 12 and 12.9 years of age, and 4.5 years for girls whose menarche occurred at 13 years of age or older (22,62).

Table 14.5 Conditions Associated with Anovulation and Abnormal Bleeding

Eating disorders

Anorexia nervosa

Bulimia nervosa

Excessive physical exercise

Chronic illness

Ovarian insufficiency/premature ovarian failure

Alcohol and other drug abuse

Stress

Thyroid disease

Hypothyroidism

Hyperthyroidism

Diabetes mellitus

Androgen excess syndromes (e.g., polycystic ovary syndrome [PCOS])

Pregnancy-related Bleeding

The possibility of pregnancy must be considered when an adolescent seeks treatment for abnormal bleeding. Bleeding in pregnancy can be associated with a spontaneous abortion, ectopic pregnancy, or other pregnancy-related complications, such as a molar pregnancy. In the United States, 31% of 15- to 17-year-old adolescent girls have had sexual intercourse, as have 69% of those 18 to 19 years old (63). Issues of confidentiality for adolescent health care are critical to an adolescent's willingness to seek appropriate reproductive health care (see Chapter 1).

Exogenous Hormones

The cause of abnormal bleeding that is experienced while an individual is taking exogenous hormones usually is very different from bleeding that occurs without hormonal manipulation (64). **Oral contraceptive use is associated with breakthrough bleeding, which occurs in as many as 30% to 40% of individuals during the first cycle of combination pill use. In addition, irregular bleeding can result from missed pills** (65,66). Strict compliance with correct and consistent pill taking is difficult for many individuals who take oral contraceptives; one study reported that only 40% of women took a pill every day (67). Other studies suggest that adolescents have an even more difficult

many missed pills, it is not surprising that some individuals experience irregular bleeding. The solution is to emphasize consistent pill taking; if the individual is unable to comply with daily pill use, an alternative contraceptive method may be preferable.

All forms of hormonal contraception, from combination and progestin-only minipills, to contraceptive patches, rings, intrauterine devices, and injectable and implantable contraception, can be associated with abnormal bleeding (69,70).

Irregular bleeding occurs frequently in users of *depomedroxyprogesterone acetate* (DMPA), although at the end of 1 year, more than 50% of users will be amenorrheic (71). Although the mechanism of bleeding associated with these hormonal methods is not well established, an atrophic endometrium or factors related to angiogenesis may be involved, suggesting options for therapy (64,72). However, it should not be assumed that any bleeding occurring while an individual is using a hormonal method of contraception is caused by that method. Other local causes of bleeding, such as cervicitis or endometritis, also can occur during use of hormone therapy (73,74).

Hematologic Abnormalities

In the adolescent age group, the possibility of a hematologic cause of abnormal bleeding must be considered. One classic study reviewed all visits by adolescent patients to an emergency room with the symptom of excessive or abnormal bleeding (Fig. 14.11) (75). The most common coagulation abnormality diagnosed was idiopathic thrombocytopenic purpura, followed by von Willebrand's disease. Von Willebrand disease occurs in approximately 1% of women in the United States and, in its mildest form, menorrhagia may be the only symptom (76). **Adolescents who have severe menorrhagia, especially at menarche, should be screened for coagulation abnormalities, including von Willebrand's disease.**

Infections

Irregular or postcoital bleeding can be associated with chlamydial cervicitis. **Adolescents have the highest rates of chlamydial infections of any age group, and sexually active teens should be screened routinely for *Chlamydia* (77). Menorrhagia can be the initial sign in patients infected with sexually transmissible organisms.** Adolescents have the highest rates of pelvic inflammatory disease (PID) of any age group of sexually experienced individuals (78) (see Chapter 16).

Other Endocrine or Systemic Problems

Abnormal bleeding can be associated with thyroid dysfunction. Signs and symptoms of thyroid disease can be somewhat subtle in teens (see Chapter 28). Hepatic dysfunction should be considered because it can lead to abnormalities in clotting factor production. Hyperprolactinemia can cause amenorrhea or irregular bleeding.

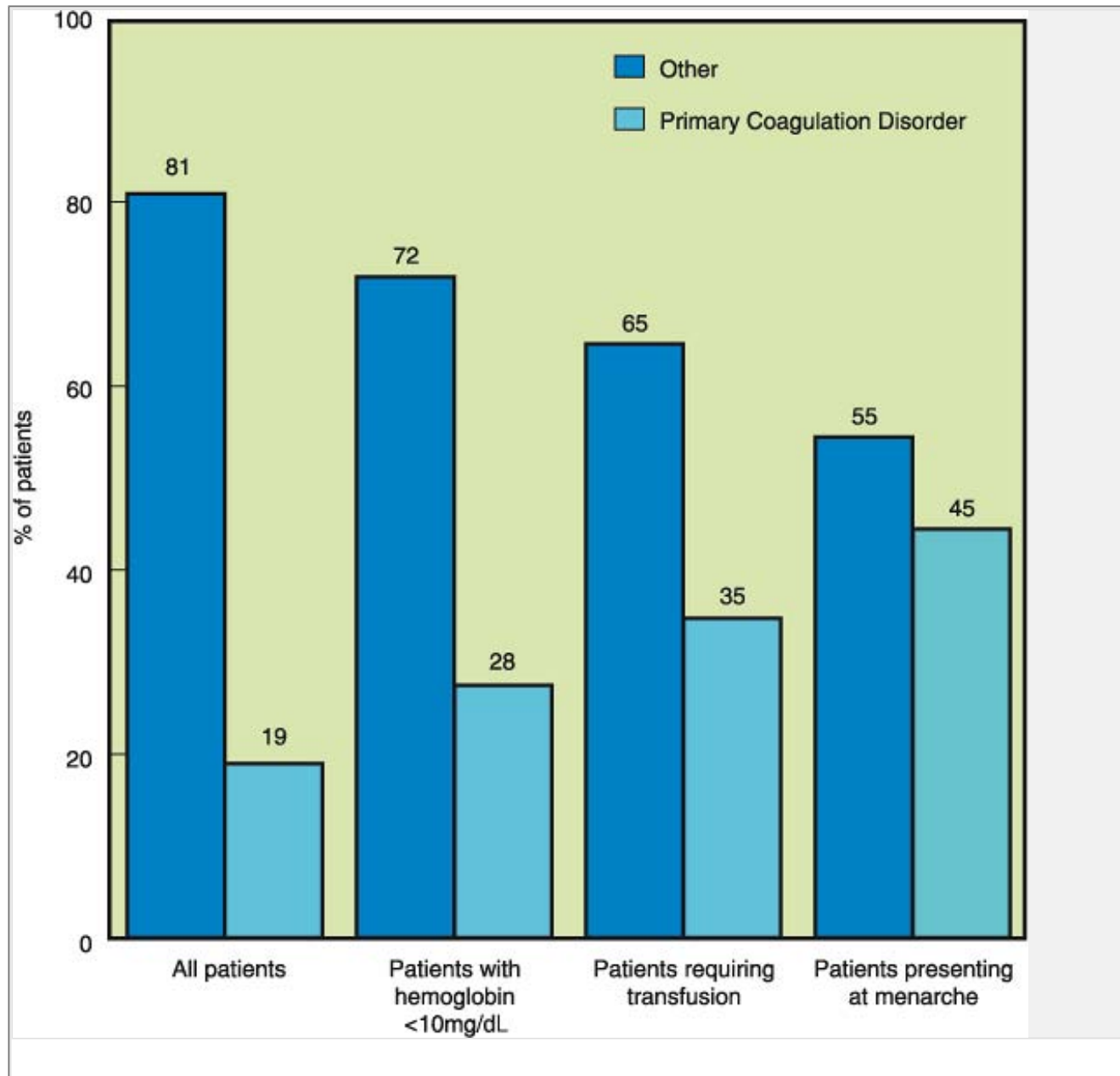


Figure 14.11 Etiology of menorrhagia in adolescents. (From **Classens AE, Cowell CA.** Acute adolescent menorrhagia. *Am J Obstet Gynecol* 1981;139:277–280, with permission.)

Polycystic ovary syndrome (PCOS) can occur during adolescence, and manifestations of excess androgen (hirsutism, acne) should prompt evaluation (79). **Androgen disorders occur in about 5% to 10% of women, making them the most common endocrine disorders in women** (see Chapter 28). **Classic PCOS, functional ovarian hyperandrogenism, or partial late-onset congenital adrenal hyperplasia all can occur in adolescence** (80). **These disorders often are overlooked, unrecognized, or untreated.** Women with even mild disorders are candidates for intervention. These disorders may be a harbinger of type 2 diabetes, endometrial cancer, and cerebrovascular disease. **Acne, hirsutism, and menstrual irregularities are often dismissed as normal during adolescence but may be manifestations of hyperandrogenism** (81,82). If an androgen abnormality is not treated, it is likely to persist beyond adolescence. Obesity, hirsutism, and acne should be evaluated to minimize the significant psychosocial costs (83). Androgenic changes are partially reversible if detected early and managed appropriately. Behavioral changes (diet and exercise) should be strongly encouraged but are often difficult to achieve. Signs of insulin resistance (acanthosis nigricans) should also be evaluated and managed appropriately (84).

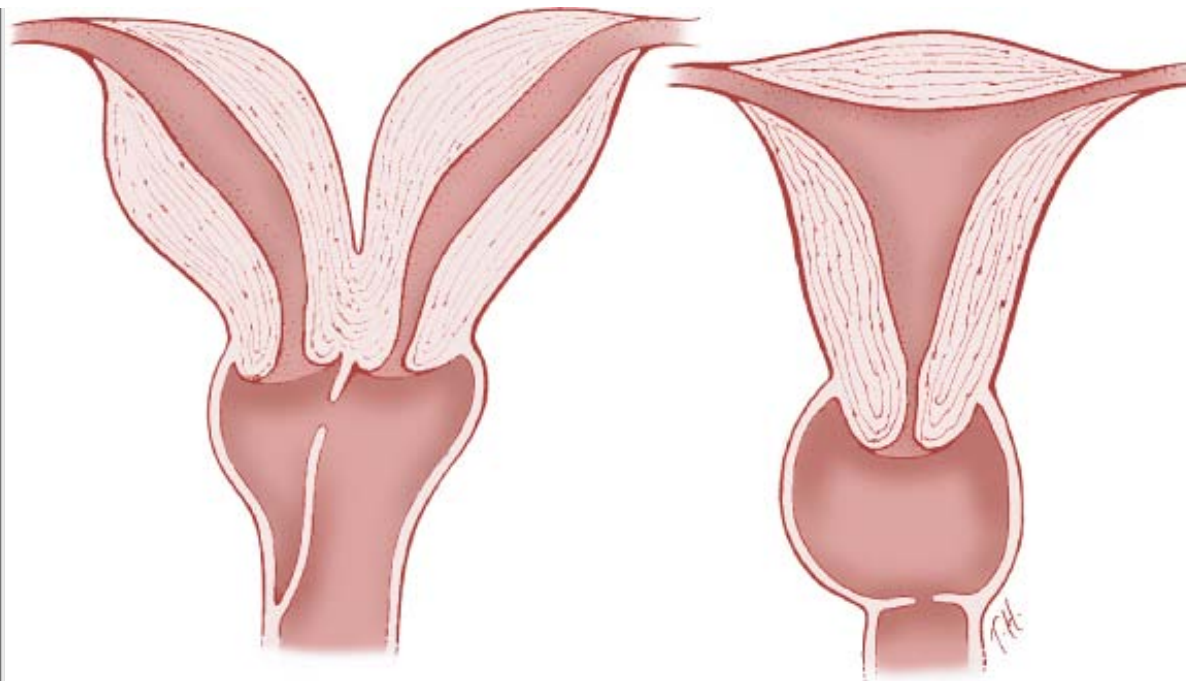


Figure 14.12 The types of obstructive or partially obstructive genital anomalies that can occur during adolescence.

Anatomic Causes

Obstructive or partially obstructive genital anomalies typically present during adolescence. Complex müllerian abnormalities, such as obstructing longitudinal vaginal septa or uterus didelphys, can cause hematocolpos or hematometra. If these obstructing anomalies have or develop a small outlet, persistent dark-brownish discharge (old blood) may appear instead of or in addition to a pelvic mass. Many varieties of uterine and vaginal anomalies exist, and clinicians who have expertise with these anomalies should be involved in their management. Fig. 14.12 illustrates situations in which abnormal bleeding can occur as a result of obstructing septa.

Diagnosis

Examination

A careful general physical examination can reveal signs of androgen excess such as

acanthosis nigricans or facial, chest/periareolar, or abdominal terminal hair growth. Because body hair is felt by many to be culturally unacceptable in women and girls, sensitive questioning about hair removal techniques (bleaching, waxing, use of depilatories, shaving, plucking) is warranted during an examination. A complete pelvic examination is appropriate in patients who have been sexually active, are having severe pain, or may have an anatomic anomaly. Testing for gonorrhea and *C. trachomatis* infection are appropriate during a speculum examination if the patient has been sexually active. Some young teens who have a history that is classic for anovulation, who deny sexual activity, and who agree to return for follow-up evaluation may be managed with a limited gynecologic examination supplemented with pelvic ultrasonography.

Laboratory Testing

Any adolescent with abnormal bleeding should undergo sensitive pregnancy testing, regardless of whether she states that she has had intercourse. The medical consequences of failing to diagnose a pregnancy are too severe to risk missing the diagnosis. Complications of pregnancy should then be managed accordingly. In addition to a pregnancy test, laboratory testing should include a complete blood count with platelet count and screening tests for coagulopathies and platelet dysfunction (85). Thyroid studies also may be appropriate. Testing for STDs may be performed as appropriate on either a cervical or a urine specimen using DNA amplification techniques. Cervical cytology testing is generally not appropriate at an emergency or urgent visit for excessive bleeding.

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Imaging Studies

If the pregnancy test results are positive, pelvic imaging using ultrasonography may be necessary to confirm a viable intrauterine pregnancy and rule out a spontaneous abortion or ectopic pregnancy. If a pelvic mass is suspected on examination, or if the examination is inadequate (more likely to be the case in an adolescent than an older woman) and additional information is required, pelvic ultrasonography may be helpful. **Although transvaginal ultrasonographic examination can be more helpful than transabdominal ultrasonography in ascertaining details of pelvic anatomy, the use of the vaginal probe may not be possible in a young girl or one who has not used tampons or had intercourse.** Direct communication between the clinician and the radiologist can be helpful in identifying candidates for transvaginal ultrasonographic examination.

Other imaging studies are not indicated as initial testing but may be helpful in selected instances.

If a pelvic ultrasonographic examination does not lead to clarification of the anatomy when vaginal septa, uterine septa, uterine duplication, or vaginal agenesis is suspected, MRI can be helpful in delineating anatomic abnormalities. This imaging technique is useful in the evaluation of uterine and vaginal developmental anomalies, although laparoscopy can still play a role in the clarification of abnormal anatomy (86,87). Computed tomography scanning may be helpful in detecting nongenital intraabdominal abnormalities.

Management

Management of bleeding abnormalities related to pregnancy, thyroid dysfunction, hepatic abnormalities, hematologic abnormalities, or androgen excess syndromes should be directed to treating the underlying condition. Oral contraceptives can be extremely helpful in managing androgen excess syndromes and other causes of anovulation (88).

Treatment with *mefenamic acid* and other nonsteroidal anti-inflammatory agents (NSAIDs) has been shown to result in decreased menstrual bleeding when compared with placebo (89). *Tranexamic acid*, an antifibrinolytic agent, has been shown to be more effective than NSAIDs, although it is not frequently used for menorrhagia in the United States. After specific diagnoses have been ruled out by appropriate laboratory testing, anovulation or dysfunctional bleeding becomes the diagnosis of exclusion. This condition can be managed either expectantly or with hormone therapy, depending on the clinical presentation and other factors, such as the need for contraception.

Anovulation: Mild Bleeding

Adolescents who have mildly abnormal bleeding, as defined by adequate hemoglobin levels and minimal disruption of daily activities, are best managed with prospective menstrual charting, frequent reassurance, close follow-up, and supplemental iron. If the patient has been bleeding heavily or for a prolonged interval, however, an apparent decrease in the bleeding does not necessarily mean that therapy is not required. This type of intermittent bleeding characterizes anovulatory bleeding and is likely to continue in the absence of therapy.

A patient who is mildly anemic will benefit from hormone therapy. If the patient is not bleeding at the time of evaluation and has no contraindications to the use of estrogen, **a combination low-dose oral contraceptive can be prescribed for use in the manner in which it is used for contraception (21 days of hormonally active pills, followed by 7 days of placebo, during which time withdrawal bleeding is expected).** If the patient is not

sexually active, she should be reevaluated after three to six cycles to determine if she desires to continue this regimen. Parents may sometimes object to the use of oral contraceptives if their daughter is not sexually active (or if they believe her not to be or even if they would like her not to be). These objections are frequently based on misconceptions about the potential risks of the pill and can be overcome by careful explanation of the pill's

role as medical therapy. If the medication is discontinued when the young woman is not sexually active and she subsequently becomes sexually active and requires contraception, it may be difficult to explain the reinstatement of oral contraceptives to the parents. If there is no significant medical or family history that would preclude their use, combination oral contraceptives are especially appropriate for the management of abnormal bleeding in adolescents for a number of reasons:

- **Approximately 50% of 17-year-old adolescent girls in the United States are sexually experienced (63).**
- **Adolescents typically wait 12 or more months after initiating sexual activity to seek medical contraception (90).**
- **At least 75% of adolescent pregnancies are unintended (91).**
- **Approximately one half of adolescent pregnancies end in abortion (92).**
- **Approximately one in three young women will experience a pregnancy before age 20 (93).**

Thus, consideration should certainly be given to continuing the oral contraception use, and parents should be reassured that the medical risks are small in otherwise healthy adolescents and that there are no significant risks associated with prolonged use. Individuals may choose to continue oral contraceptives for contraception or their noncontraceptive benefits (improvement of acne, decreased dysmenorrhea, and lighter, more regular menstrual flow).

Sometimes, providing parents with accurate information about the safety of oral contraceptives, emphasizing that currently available oral contraceptive preparations contain lower doses of estrogens and progestins than those used in the 1960s and 1970s, and

emphasizing the hormonal rather than contraceptive function, may not be persuasive. In such cases, cyclic progestins are an alternative. A systematic review of the use of combination hormonal therapy versus progestins alone for the treatment of anovulatory bleeding found a paucity of evidence supporting the efficacy of one management regimen over the other (94). **Medroxyprogesterone acetate, 5 to 10 mg/day for 10 to 13 days every 1 to 2 months, prevents excessive endometrial buildup and irregular shedding caused by unopposed estrogen stimulation.** This therapy also should be reevaluated regularly and accompanied by oral administration of iron. Eventual maturation of the hypothalamic–pituitary–ovarian axis usually will result in the establishment of regular menses unless there are underlying conditions such as hyperandrogenism.

Acute Bleeding

Moderate

Patients who are bleeding acutely but in a stable condition and do not require hospital admission will require doses of hormones that are higher than those in oral contraceptives to effectively stop anovulatory bleeding. An effective regimen is the use of combination monophasic oral contraceptives (every 6 hours for 4 to 7 days). After that time, the dose should be tapered or stopped to allow withdrawal flow. With this therapy, the patient and her parents should be given specific written and oral instructions warning them about the potential side effects of high-dose hormone therapy—nausea, breast tenderness, and breakthrough bleeding. The patient should be instructed to call with any concerns rather than discontinue the pills, and she must understand that stopping the prescribed regimen may result in a recurrence of heavy bleeding. Both the patient and her mother should be warned to expect heavy withdrawal flow for the first period. It will be controlled by the institution of combination low-dose oral contraceptive therapy given once daily and continued for three to six cycles to allow regular withdrawal flow. If

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the patient is not sexually active, the pill may be discontinued and the menstrual cycles may be reassessed.

Emergency Management

The decision to hospitalize a patient depends on the rate of current bleeding and the severity of any existing anemia. The actual acute blood loss may not adequately be reflected in the initial blood count but will be revealed with serial

hemoglobin assessments. The cause of acute menorrhagia may be a primary coagulation disorder (75); thus, measurements of coagulation and hemostasis, including screening for coagulopathy, should be performed for any adolescent patients with acute menorrhagia. The method of screening depends on the laboratory tests that are available; the use of a platelet function analyzer has been described as a reasonable screening tool (95). Von Willebrand's disease, platelet disorders, or hematologic malignancies can cause menorrhagia in adolescents. Depending on the patient's level of hemodynamic stability or compromise, a blood sample can be analyzed for type and screen. The decision to transfuse must be considered carefully, and the benefits and risks should be discussed with the adolescent and her parents. Generally, there is no need for transfusion unless the patient is hemodynamically unstable.

In patients who, by exclusion, have been diagnosed as having dysfunctional bleeding, hormone therapy usually makes it possible to avoid surgical intervention (dilation and curettage [D & C], operative hysteroscopy, or laparoscopy).

A patient who has been hospitalized for severe bleeding requires aggressive management as follows:

- **After stabilization, when appropriate laboratory assessment and an examination have established a working diagnosis of anovulation, hormonal management will usually control bleeding.**
- ***Conjugated estrogens*, either 25 to 40 mg given intravenously every 6 hours or 2.5 mg given orally every 6 hours, will usually be effective.**
- **If estrogens are not effective, the patient should be reevaluated and the diagnosis should be reassessed.** The failure of hormonal management suggests that a local cause of bleeding is more likely. In this event, consideration should be given to a pelvic ultrasonographic examination to determine any unusual causes of bleeding (such as uterine leiomyomas or endometrial hyperplasia) and to assess the presence of intrauterine clots that may impair uterine contractility and prolong the bleeding episode.
- **If intrauterine clots are detected, evacuation of the clots (suction curettage or D & C) is indicated.** Although a D & C will provide effective immediate control of the bleeding, it is unusual to reach this step in adolescents.

More drastic forms of treatment other than a D & C (such as ablation of the endometrium by laser or cryotherapy) are considered inappropriate for adolescents because of concerns about future fertility.

If intravenous or oral administration of estrogen controls the bleeding, oral progestin therapy should be instituted and continued for several days to stabilize the endometrium. This therapy can be accomplished by using a combination oral contraceptive, usually one with 30 to 35 mg of estrogen, or by using the tapering regimen previously described. The medication can be tapered and ultimately stopped to allow withdrawal bleeding. Low-dose combination oral contraception should be continued for three to six cycles, or longer if desired, to provide normal menstrual cycles.

In general, the prognosis for regular ovulatory cycles and subsequent normal fertility in young women who experience an episode of abnormal bleeding is good, particularly for

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patients who develop abnormal bleeding as a result of anovulation within the first years after menarche and in whom there are no signs of other specific conditions. Some girls, including those in whom there is an underlying medical cause, such as PCOS, will continue to have abnormal bleeding into middle and late adolescence and adulthood and will benefit from the ongoing use of oral contraceptives to manage hirsutism, acne, and irregular periods. Ovulation induction may be necessary to achieve fertility in these individuals. Girls with coagulopathies also may benefit from ongoing oral contraceptive use.

Long-term Menstrual Suppression

For patients with underlying medical conditions, such as coagulopathies or a malignancy requiring chemotherapy, long-term therapeutic amenorrhea with menstrual suppression using the following regimens may be necessary:

- Progestins such as oral *norethindrone*, *norethindrone acetate*, or *medroxyprogesterone acetate* on a continuous daily basis
- Continuous (noncyclic) combination regimens of oral estrogen and progestins (birth control pills) that do not include a withdrawal bleeding–placebo week
- Depot formulations of progestins (DMPA), with or without concurrent estrogens

- Gonadotropin-releasing hormone (GnRH) analogs with or without estrogen add-back therapy
- *Levonorgestrel* intrauterine system (IUS)

The choice of regimen depends on the presence of any contraindications (such as active liver disease precluding the use of estrogens) and the clinician's experience. **Although the goal of these long-term suppressive therapies is amenorrhea, all of these regimens may be accompanied by breakthrough bleeding.** At 1 year, rates of amenorrhea approach 90% with extended cycle combination oral contraceptives, 50% with DMPA, and 50% with the *levonorgestrel* IUS (96,97,98). Because both DMPA and GnRH analogs have been associated with disadvantageous effects on bone mineral density, the potential risks must be weighed against their medical benefits (99,100). Regular follow-up visits and continued patient encouragement are required with all of these options. Occasional episodes of spotting and mild breakthrough bleeding that do not result in a lowered hemoglobin level may be managed expectantly. When breakthrough bleeding affects the hemoglobin level, it should be evaluated with respect to the underlying disease. For example, in a patient with underlying platelet dysfunction, breakthrough bleeding may reflect a lowered platelet count. Bleeding in a patient with hepatic disease may reflect worsening hepatic function. Supplemental low-dose estrogen can be helpful in the management of excessive breakthrough bleeding that has no specific cause other than the hormone therapy.

Pelvic Masses

Presentation

Adolescents with pelvic masses may be asymptomatic or may have chronic or acute symptoms. An ovarian mass may be discovered incidentally when an ultrasonographic examination is performed to evaluate the urinary system or when imaging is performed to evaluate pelvic pain. The mere presence of a mass on imaging studies does not always indicate that the mass is the cause of pelvic pain. **A "ruptured ovarian cyst" is a classic diagnosis when an adolescent presents with pelvic pain, even if ultrasonography findings suggest only a simple cystic follicle and a physiologic amount of pelvic fluid that are unlikely to cause pain.** Alternatively, ovarian masses can cause severe acute or intermittent symptoms caused by torsion (Fig. 14.13), intraperitoneal rupture, or bleeding into the ovarian tissue. These conditions can represent a true surgical emergency or urgency, and their diagnosis can

be challenging. The pressure of an enlarging ovarian mass can cause bowel-related symptoms such as constipation, vague discomfort, and early satiety; urinary frequency; or even ureteral or bladder neck obstruction.



Figure 14.13 Adnexal mass with torsion.

Diagnosis

The history and pelvic examination are critical in the diagnosis of a pelvic mass. Considerations in adolescents include the anxiety associated with a first pelvic examination, as well as issues of confidentiality related to questions about sexual activity. Techniques for history taking and

the performance of the first examination are discussed in Chapter 1.

Laboratory studies should always include a pregnancy test (regardless of stated sexual activity), and a complete blood count may be helpful in diagnosing inflammatory masses. Tumor markers, including α -fetoprotein and human chorionic gonadotropin (hCG), may be elaborated by germ cell tumors and can be useful in preoperative diagnosis as well as follow-up (see Chapter 32).

As in all age groups, the primary diagnostic technique for evaluating pelvic masses in adolescents is ultrasonography. Although transvaginal ultrasonographic examinations may provide more detail than transabdominal ultrasonography, particularly with inflammatory masses, a transvaginal examination may not be well tolerated by adolescents (101). Ultrasonography usually is the most helpful imaging technique for assessing ovarian masses. **For cases in which the suspected diagnosis is appendicitis or another nongynecologic condition, or if the results of the ultrasonographic examination are inconclusive, CT or MRI may be helpful.** An accurate preoperative assessment of anatomy is critical, particularly in cases of uterovaginal malformations. Magnetic resonance imaging can be useful for evaluating this group of rare anomalies (102,103). Adolescents who present with abdominal pain should be evaluated with some type of imaging procedure

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because an unexpected finding of a complex uterine or vaginal anomaly requires careful surgical planning and management.

Differential Diagnosis

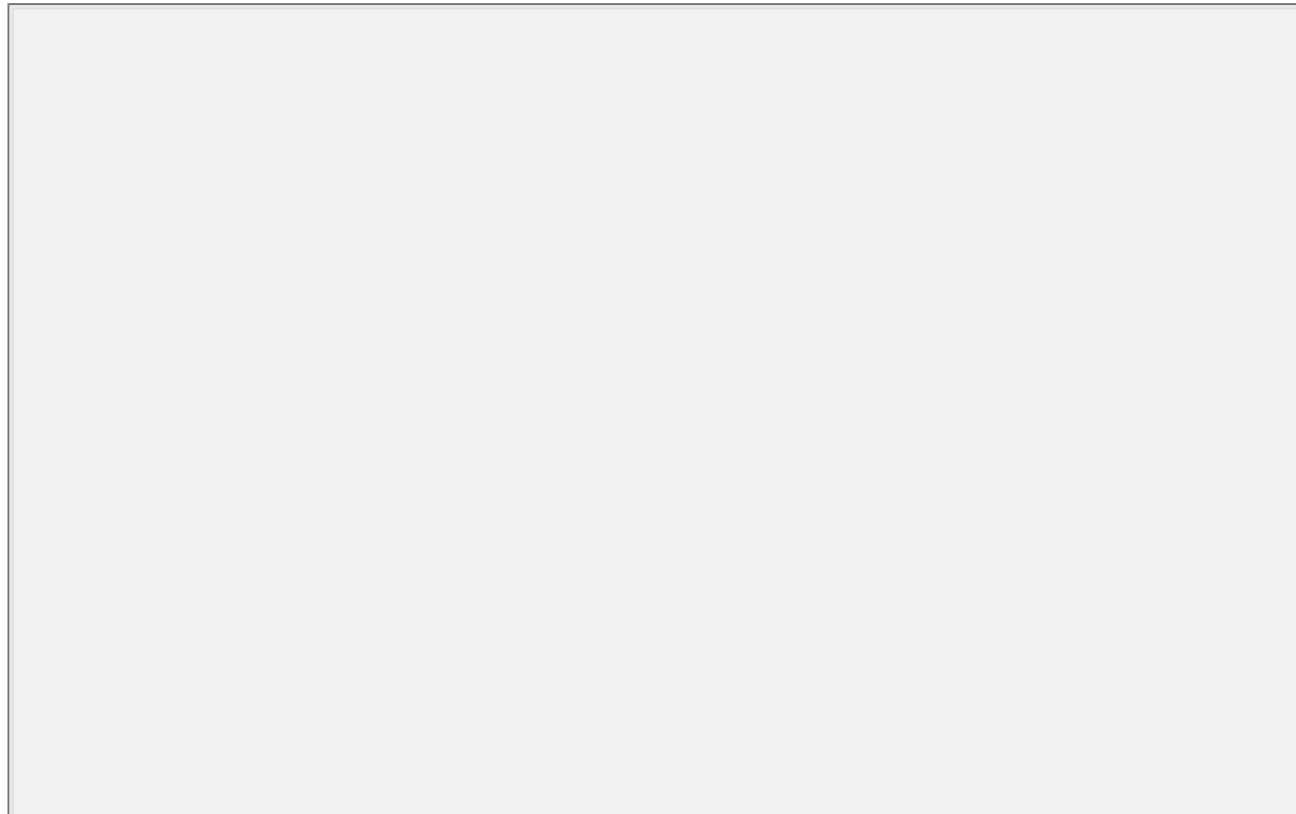
Ovarian Masses

Many studies of ovarian tumors in the pediatric and adolescent age group do not distinguish between prepubertal/premenarchal girls and menarchal adolescents. The findings of some reports are based on age group, although this is less helpful than a distinction by pubertal development. In evaluating a pelvic or abdominal mass, the clinician must take into consideration the patient's pubertal status because the likelihood of functional masses increases after menarche. **The risk of malignant neoplasms is lower among adolescents than among younger children. Epithelial neoplasms occur with increasing frequency with age. Germ cell tumors are the most common tumors of the first decade of life but occur less frequently during adolescence** (see Chapter 35). **Mature cystic teratoma is the most frequent neoplastic tumor of children and adolescents, accounting for**

more than one half of ovarian neoplasms in women younger than 20 years of age (104).

It is well established that neoplasia can arise in dysgenetic gonads. Malignant tumors have been found in about 25% of dysgenetic gonads of patients with a Y chromosome (105). Gonadectomy is recommended during adolescence after the attainment of pubertal development for patients with XY gonadal dysgenesis or its mosaic variations (106).

Functional ovarian cysts occur frequently in adolescence. They may be an incidental finding on examination or may be associated with pain caused by torsion, leakage, or rupture. Paratubal cysts represent embryologic remnants that may be confused with an ovarian mass (Fig. 14.14); they are typically asymptomatic, but can be associated with adnexal torsion. Endometriosis is less common during adolescence than in adulthood, although it can occur during adolescence. In one study of adolescents referred with chronic pain, 50% to 65% were found to have endometriosis (107). Although endometriosis can occur in young women with obstructive genital anomalies (presumably as a result of retrograde menstruation), most adolescents with endometriosis do not have associated obstructive anomalies (108). In young women, endometriosis may have an atypical appearance characterized by nonpigmented or vesicular lesions, peritoneal windows, and puckering (109).



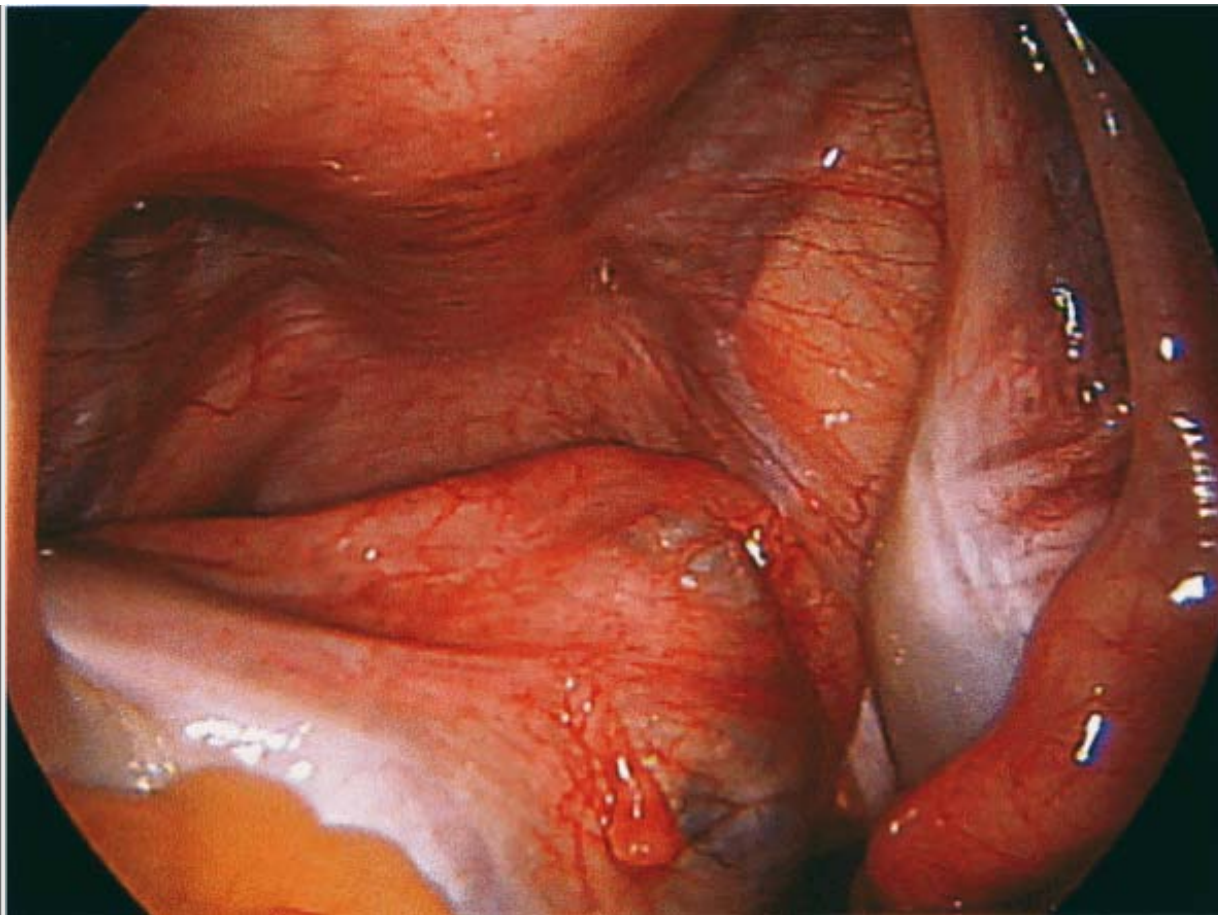


Figure 14.14 Paratubal cyst.

Uterine Masses

Other causes of pelvic masses, such as uterine abnormalities, are rare in adolescence. Uterine leiomyomas are not often seen in this age group. Obstructive uterovaginal anomalies occur during adolescence, at the time of menarche, or shortly thereafter. The diagnosis is frequently is either not suspected or delayed (110). A wide range of anomalies can occur, from imperforate hymen to transverse vaginal septa, to vaginal agenesis with a normal uterus and functional endometrium, vaginal duplications with obstructing longitudinal septa, and obstructed uterine horns (Fig. 14.12). Patients may seek treatment for cyclic pain; amenorrhea; vaginal discharge; or an abdominal, pelvic, or

vaginal mass. A hematocolpos, hematometra, or both frequently will be present, and the resulting mass can be quite large (111).

Inflammatory Masses

Of all age groups of sexually active women, adolescents have the highest rates of PID (78). Thus, an adolescent who has pelvic pain may be found to have an inflammatory mass. Such masses may consist of a tubo-ovarian complex (a mass of matted bowel, tube, and ovary), tubo-ovarian abscess (a mass consisting primarily of an abscess cavity within an anatomically defined structure such as the ovary), pyosalpinx, or, chronically, hydrosalpinx.

The diagnosis of PID is primarily a clinical one based on the presence of lower abdominal, pelvic, and adnexal tenderness; cervical motion tenderness; a mucopurulent discharge; and elevated temperature, white blood cell count, or sedimentation rate (see Chapter 16). The risk of PID is clearly associated with that of acquiring STDs, and methods of contraception may either decrease the risk (oral contraceptives, male latex condoms) or increase it (the intrauterine device in the interval immediately after insertion) (112,113,114).

Pregnancy

In adolescents, pregnancy should always be considered as a cause of a pelvic mass. In the United States, approximately 50% of adolescent young women have experienced sexual intercourse (63). Most pregnancies in adolescents are unintended; 82% of pregnancies in adolescents younger than age 15, 83% in women aged 15 to 17, and 75% in women aged 18 to 19 are unintended (91). Adolescents may be more likely than adults to deny the possibility of pregnancy because of wishful thinking, anxiety about discovery by parents or peers, or unfamiliarity with menstrual cycles and information about fertility. Ectopic pregnancies may cause pelvic pain and an adnexal mass. With the availability of quantitative measurements of β -hCG, more ectopic pregnancies are being discovered before rupture, allowing conservative management with laparoscopic surgery or medical therapy with *methotrexate* (see Chapter 18). The risk of ectopic pregnancy varies by method of contraception; users of no contraception have the highest risk, whereas oral contraceptive users have the lowest risk (115). As with older patients, paraovarian cysts and nongynecologic masses can appear as a pelvic or abdominal mass in adolescents.

Management

The management of masses in adolescents depends on the suspected diagnosis as well as the initial symptom. Figure 14.8 outlines a plan of management for pelvic masses in

adolescents. **Asymptomatic unilocular cystic masses are best managed conservatively because the likelihood of malignancy is low. If surgical management is required based on symptoms or uncertainty of diagnosis, attention should be directed to minimizing the risks of subsequent infertility resulting from pelvic adhesions. In addition, every effort should be made to conserve ovarian tissue. In the presence of a malignant unilateral ovarian mass, management may include unilateral oophorectomy rather than more radical surgery, even if the ovarian tumor has metastasized (see Chapter 35). Analysis of frozen sections may not be reliable. In general, conservative surgery is appropriate; further surgery can be performed, if necessary, after an adequate histologic evaluation of the ovarian tumor.**

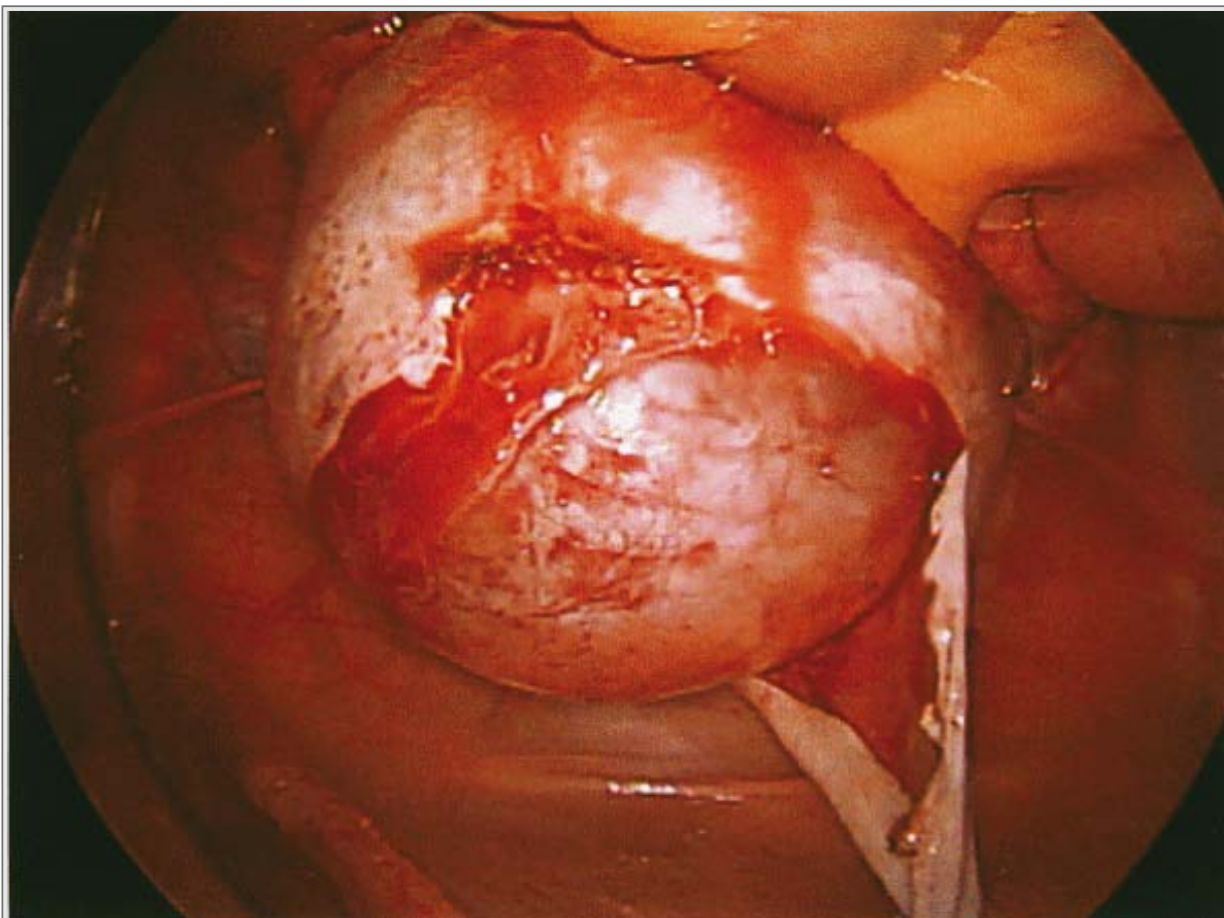


Figure 14.15 Laparoscopic paratubal cystectomy.

Some surgeons advocate the use of laparoscopy in the management of suspected acute PID to confirm the diagnosis and to perform irrigation, lysis of adhesions, drainage and irrigation of unilateral or bilateral pyosalpinx or tubo-ovarian abscess, or extirpation of significant disease (Fig. 14.15) (116,117). **When symptoms persist in a patient with the clinical diagnosis of PID or tubo-ovarian abscess, laparoscopy should be considered to confirm the diagnosis. A clinical diagnosis may be incorrect in as many as one third of patients (118). The surgical management of inflammatory masses is rarely necessary in adolescents, except to treat rupture of tubo-ovarian abscess or failure of medical management with broad-spectrum antibiotics** (see Chapter 16).

Conservative, unilateral adnexectomy usually can be performed in these situations, rather than a pelvic clean-out, maintaining reproductive potential. Percutaneous drainage, transvaginal ultrasonographic drainage, and laparoscopic management of tubo-ovarian abscesses are being done more often. As with the laparoscopic management of ovarian masses, the surgeon's skill and experience with this procedure are critical, and prospective studies on its effectiveness are lacking (119). Laparoscopic management has been associated with a risk of major complications, including bowel obstruction and bowel or vessel injury (120).

Vulvar Conditions

Adolescents with gonadal dysgenesis or androgen insensitivity may have abnormal pubertal development and primary amenorrhea (see Chapter 27).

Various developmental abnormalities—vaginal agenesis, imperforate hymen, transverse and longitudinal

vaginal septa, vaginal and uterine duplications, hymenal bands, and septa—most often occur in early adolescents with amenorrhea (for the obstructing abnormalities) or with concerns such as inability to use tampons (for hymenal and vaginal bands and septa). These developmental abnormalities must be evaluated carefully to determine both external and internal anatomy.

A tight hymenal ring may be discovered when the patient seeks care because of concerns about the inability to use tampons or have intercourse. Both manual dilation and small relaxing incisions at 6 o'clock and 8 o'clock in the hymenal ring can be effective. This procedure can sometimes be done in the office using local anesthesia but may require conduction or general anesthesia in the operating room. Hymenal bands are not rare and also lead to difficulty in using tampons; they usually can be incised in the office using local anesthetic. Hypertrophy of the labia minora is a developmental abnormality that can be corrected surgically (121). This condition is more appropriately considered a variant of

normal, and reassurance rather than a cosmetic surgical reduction is appropriate as the primary therapy. Genital ulcerations may occur in girls with leukemia or other cancers requiring chemotherapy (122). The possibility of sexual abuse, incest, or involuntary intercourse should be considered for young adolescents with vulvovaginal symptoms, STDs, or pregnancy.

The presence of vulvar symptoms such as itching or burning may prompt a patient to seek care; however, this anatomic site is not one that is easily inspected by the patient. Thus, vulvar lesions may be found on examination and may not have been noticed by the patient.

Vulvar self-examination should be encouraged and could potentially result in the earlier diagnosis of vulvar lesions such as melanoma (123). Adolescents presenting with vulvar itching may have lichen sclerosus; this condition can also be relatively asymptomatic, even when an examination reveals loss of anatomic structures and scarring (10).

Adolescents as well as adults often incorrectly self-diagnose vulvovaginal candidiasis; in one study, only one third of women with self-diagnosed yeast vaginitis were found to have this infection (124) (see Chapter 16). A clinical examination and appropriate testing can be performed even on young adolescents using a cotton swab to obtain vaginal secretions for pH testing and microscopic examination.

Vulvar condylomata are an extremely common cause of vulvar lesions in adolescents (see Chapter 16). Genital warts can affect the vulva, perineum, and perianal skin, as well as the vagina, urethra, and anus (Fig. 14.16). They may be asymptomatic or cause symptoms of itching, irritation, or bleeding. Symptomatic, enlarging, or extensive vulvar condylomata can be managed with topical medication applied by the patient or clinician (77). The choice of treatment should be guided by patient preference, available resources, and the clinician's experience; no one treatment has been found to be superior to the others (77).

Vaginal Conditions

Vulvovaginal symptoms in adolescents may be caused by a variety of conditions, ranging from vulvar lichen sclerosus to urinary tract infection to *Chlamydia trachomatis* to non-STD-related vaginitis. Urinary or vaginal symptoms do not differentiate well between urinary tract infections (UTIs) and vaginitis. Adolescent girls who are screened for both *Chlamydia trachomatis* and UTI have high rates of concurrent disease (125). Because clinical diagnosis based on symptoms is imprecise, female adolescent with vaginal or urinary symptoms should be tested for both *Chlamydia trachomatis* and UTI. Testing with DNA-based procedures may be performed on samples obtained from the cervix, from swabs of vaginal secretions (either clinician or patient obtained), and from urine specimens. Testing that does not involve a speculum examination may be particularly helpful for adolescents: a

recent rigorous review concluded that noninvasive *Chlamydia* testing was comparable to cervical or urethral screening, although this was not the case with testing for gonorrhea (126).



Figure 14.16 Extensive vulvar condyloma.

Discharge is one of the most common vaginal symptoms. Conditions ranging from vaginal candidiasis to chlamydia cervicitis to bacterial vaginosis may cause vaginal discharge in adolescents. Infectious vaginal conditions are described in more detail in Chapter 16. The risks of self-diagnosis of vaginal discharge in adolescents may be greater than in adult women, as infection with STDs—including *Neisseria gonorrhoea*, *Trichomonas vaginalis*, *Chlamydia trachomatis*, herpes simplex, and *condyloma acuminata*—are common in adolescents and may be less likely to be recognized as such.

Use of vaginal tampons has been associated with both microscopic and macroscopic ulcerations. Healing of the macroscopic ulcerations occurs within several weeks without specific therapy if tampon use is suspended. A follow-up examination to demonstrate healing is appropriate, with biopsy of any persistent ulcerations to rule out other lesions.

Toxic shock syndrome (TSS) has been associated with tampon use and vaginal exotoxins produced by *Staphylococcus aureus*. This syndrome consists of fever, hypotension, a diffuse erythroderma with desquamation of the palms and soles, plus involvement of at least three major organ systems (127). Vaginal involvement includes mucous membrane inflammation. The frequency of TSS appears to be declining, and an increasing percentage of cases are not associated with menses (128). Currently, approximately one half of all cases of TSS are menstrual related (128). Epidemiologic studies have suggested that adolescents are at greater risk of menstrual TSS than older women; however, this finding does not appear to be explained by differences in the detection of antibodies to the TSST-1 toxin-producing strain of *S. Aureus* or in *S. Aureus* vaginal colonization rates (129).

Abscesses of Bartholin and Skene's glands are related to both aerobic and anaerobic organisms, with mixed infections accounting for approximately 60% of these and other vulvar and labial abscesses (130). Therapy consists of surgical drainage, with use of antibiotics a secondary measure. In younger adolescents, incision and drainage with insertion of a Word indwelling catheter may require general anesthesia.

Reproductive Age Group

Abnormal Bleeding

Normal Menses

After adolescence, menstrual cycles generally conform to a cycle length of 21 to 35 days, with a duration of fewer than 7 days of menstrual flow. As a woman approaches menopause, cycle length becomes more irregular as fewer cycles are ovulatory (54). The most frequent cause of irregular bleeding in the reproductive age group is hormonal, although other causes such as pregnancy-related bleeding (spontaneous abortion, ectopic pregnancy) should always be considered. Although a variety of terms have been used to describe abnormal menses (Table 14.6), accurate characterization of the bleeding based on records (preferably charted prospectively) may be more important than the use

of specific terms. **The mean duration of menses is 4.7 days; 89% of cycles last 7 days or longer. The average blood loss per cycle is 35 mL (58). Menses is a suspension of blood- and tissue-derived solids within a mixture of serum and cervicovaginal fluid; the blood content of menses varies over the days of bleeding, but on average is close to 50% (131). Recurrent bleeding in excess of 80 mL/cycle results in anemia.**

Differential Diagnosis

Dysfunctional Uterine Bleeding

The term *dysfunctional uterine bleeding* has been used to describe abnormal bleeding for which no specific cause has been found. It most often implies a mechanism of anovulation, although not all bleeding that is outside the normal range (in either cycle length or duration) is anovulatory. The term is a diagnosis of exclusion, which is probably more confusing than enlightening. Other terms that are commonly used to describe bleeding abnormalities include *anovulatory uterine bleeding* and *abnormal uterine bleeding* (132).

Most anovulatory bleeding is a result of what has been termed *estrogen breakthrough*. In the absence of ovulation and the production of progesterone, the endometrium responds to estrogen stimulation with proliferation. This endometrial growth without periodic shedding results in eventual breakdown of the fragile endometrial tissue. Healing within the endometrium is irregular and dyssynchronous. Relatively low levels of estrogen stimulation will result in irregular and prolonged bleeding, whereas higher sustained levels result in episodes of amenorrhea followed by acute, heavy bleeding.

Pregnancy-related Bleeding

Spontaneous abortion can be associated with excessive or prolonged bleeding. A woman may be unaware that she has conceived and may seek care because of abnormal bleeding. In the United States, more than 50% of pregnancies are unintended (91), and 10% of women are at risk for unintended pregnancy but use no method of contraception. These women may be at particular risk for bleeding related to an unsuspected pregnancy. About one half of unintended pregnancies are a result of nonuse of contraception; however, the other one half are contraceptive failures (90). **Unintended pregnancies are most likely to occur among adolescents and women older than 40 years of age** (see Chapter 10). If an ectopic pregnancy is ruled out, the management of spontaneous abortion may include either observation, if the bleeding is not excessive, medical or pharmacologic uterine evacuation,

or surgical management with suction curettage or D & C, depending on the clinician's judgment and the patient's preference (133,134,135). Surgical management appears to be the most likely to result in complete evacuation; lower rates of success are seen with both medical and expectant management, although the type of miscarriage and gestational age affect these rates (136) (see Chapter 18).

Table 14.6 Abnormal Menses—Terminology

<i>Term</i>	<i>Interval</i>	<i>Duration</i>	<i>Amount</i>
Menorrhagia	Regular	Prolonged	Excessive
Metrorrhagia	Irregular	±Prolonged	Normal
Menometrorrhagia	Irregular	Prolonged	Excessive
Hypermenorrhea	Regular	Normal	Excessive
Hypomenorrhea	Regular	Normal or less	Less
Oligomenorrhea	Infrequent or irregular	Variable	Scanty
Amenorrhea	Absent	No menses for 90 d	Absent

Exogenous Hormones

Irregular bleeding that occurs while a woman is using contraceptive hormones should be considered in a different context than bleeding that occurs in the absence of exogenous hormone use. Breakthrough bleeding during the first 1 to 3 months of oral contraceptive use occurs in as many as 30% to 40% of users; it should almost always be managed expectantly with reassurance because the frequency of breakthrough bleeding decreases with each subsequent month of use (65).

Irregular bleeding can also result from inconsistent use (137,138,139). Other estrogen-progestin delivery systems, including the contraceptive patch, vaginal ring, and intramuscular regimens, also are associated with irregular breakthrough bleeding (140).

These nondaily contraceptive regimens may promote successful compliance, making irregular bleeding a less important factor for some women in assessing the balance of risks versus benefits (141) (see Chapter 10).

Use of progestin-only methods—including DMPA, progestin-only pills, the contraceptive implant,

and the *levonorgestrel* IUS—is associated with relatively high rates of initial irregular and unpredictable bleeding; rates of amenorrhea vary over time and by method (142). Because irregular bleeding is so often present with these two methods of contraception, counseling before their use is imperative. Women who do not believe that they can cope with irregular, unpredictable bleeding may not be good candidates for these methods.

The management of irregular bleeding with hormonal contraceptive use can range from reassurance and expectant management initially to recommendations for a change in the hormonal delivery system or regimen. The use of additional oral estrogen has been reported to improve bleeding with both DMPA and the subdermal *levonorgestrel* (71,143,144). The use of NSAIDs has also been shown to result in decreased breakthrough bleeding (143). The development of a better understanding of the mechanisms causing irregular bleeding will likely result in more effective and acceptable management strategies (145).

Not all bleeding that occurs while an individual is using hormonal contraception is a consequence of hormonal factors. In one study, women who experienced irregular bleeding while taking oral contraceptives were found to have a higher frequency of *C. trachomatis* infection (73). Thus, screening should be considered in women presenting with irregular bleeding while using hormonal contraception.

Endocrine Causes

Both hypothyroidism and hyperthyroidism can be associated with abnormal bleeding. With hypothyroidism, menstrual abnormalities, including menorrhagia, are common (see Chapter 28). The most common cause of thyroid hyper-functioning in premenopausal women is Graves' disease, which occurs four to five times more often in women than men. Hyperthyroidism can result in oligomenorrhea or amenorrhea, and it also can lead to elevated levels of plasma estrogen (146). Other causes of anovulation include hypothalamic dysfunction, hyperprolactinemia, premature ovarian failure, and primary pituitary disease (132). Although these conditions often are considered as causes of amenorrhea (see Chapter 27), irregular bleeding also may result in their presence.

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The rare and unusual causes of abnormal bleeding should not be overlooked. Women with premature ovarian failure frequently see several clinicians, and the diagnosis is often delayed during waning ovarian function and insufficiency (147,148). For this reason, some clinicians have urged that women be encouraged to track their menstrual cyclicity and to consider that the menstrual cycle can be a "vital sign" that reflects overall health.

Diabetes mellitus can be associated with anovulation, obesity, insulin resistance,

and androgen excess. Androgen disorders are very common among women of reproductive age and should be evaluated and managed accordingly. Polycystic ovary syndrome is present in 5% to 8% of adult women and undiagnosed in many women (149). Because androgen disorders are associated with significant cardiovascular disease, the condition should be diagnosed promptly and treated. This condition becomes of more immediate concern in older women of reproductive age. Management of bleeding disorders associated with androgen excess consists of an appropriate diagnostic evaluation followed by the use of oral contraceptives (in the absence of significant contraindications or the desire for conception) or the use of insulin-sensitizing agents, coupled with dietary and exercise modification (150).

Anatomic Causes

Anatomic causes of abnormal bleeding occur more frequently in women of reproductive age than in women in other age groups. Uterine leiomyomas and endometrial polyps are common conditions that most often are asymptomatic; however, they remain important causes of abnormal bleeding (151). Uterine leiomyomas occur in as many as one half of all women older than age 35 years and are the most common tumors of the genital tract (151,152). One study of a randomly selected population estimated a cumulative prevalence of greater than 80% in black women and nearly 70% in white women (153). Leiomyomas are estimated to be clinically significant in at least 25% of women of reproductive age in the United States. They are more common in African-American women than white women and have been associated with obesity (154,155) Abnormal bleeding is the most common symptom for women with leiomyomas. Although the number of uterine leiomyomas and their size do not appear to influence the occurrence of abnormal bleeding, submucosal myomas are the most likely to cause bleeding.

The mechanism of abnormal bleeding related to leiomyomas is not well established. Several theories have been postulated, including dysregulation of a number of growth factors that regulate angiogenesis in a uterus in which leiomyomas are present. Growth factors that are currently being investigated for their role in the process of abnormal bleeding associated with leiomyomas include basic fibroblast growth factor, vascular endothelial growth factor, heparin-binding epidermal growth factor, platelet-derived growth factor, transforming growth factor- β , parathyroid hormone-related protein, and prolactin (156).

Endometrial polyps are a cause of intermenstrual bleeding, irregular bleeding, and menorrhagia, although as with leiomyomas, most endometrial polyps are asymptomatic. Endometrial polyps can cause menorrhagia and metrorrhagia, and they may be associated with dysmenorrhea. The incidence of endometrial polyps increases with age throughout the reproductive years (151). The diagnosis is based on either visualization

with hysteroscopy or sonohysterography or the microscopic assessment of tissue obtained by a biopsy done in the office or a curettage specimen. One study using sonohysterography found polyps in 33% of symptomatic premenopausal women older than the age of 29 years who were experiencing abnormal bleeding versus 10% in asymptomatic women (157). In this study, polyps also were associated with leiomyomas, both intracavitary and intramural, which were present in 13% and 58%, respectively, of symptomatic women with bleeding. Endometrial polyps can regress spontaneously. In one study in which asymptomatic women underwent repeat sonohysterography after 2.5 years, four of seven polyps resolved; these polyps tended to be smaller than those that did not resolve (158). The larger polyps were more likely to result in abnormal bleeding. Whereas polyps may

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resolve spontaneously over time, a clinically important question is whether they are likely to undergo malignant transformation. Because even asymptomatic polyps usually are removed at the time of identification, this question is difficult to answer. A review the pathology of resected polyps suggests that the chance of malignancy is less than 5% and likely approximates 0.5% (151). In one large series, it was rare to find atypia or carcinoma in an endometrial polyp from a premenopausal woman (159).

Abnormal bleeding, either intermenstrual or postcoital, can be caused by cervical lesions. Bleeding can also result from endocervical polyps and infectious cervical lesions, such as condylomata, herpes simplex virus ulcerations, chlamydial cervicitis, or cervicitis caused by other organisms. Other benign cervical lesions, such as wide eversion of endocervical columnar epithelium or nabothian cysts, may be detected on examination but rarely cause bleeding.

Coagulopathies and Other Hematologic Causes

The presence of excessively heavy menses should prompt an evaluation of hematologic status. A complete blood count will be helpful in detecting anemia, significant problems such as leukemia, or disorders associated with thrombocytopenia. Abnormal liver function, which can be seen with alcoholism or other chronic liver diseases, results in inadequate production of clotting factors and can lead to excessive menstrual bleeding. Coagulation abnormalities such as von Willebrand's disease, occurring in up to 1% of the population, can have a variable clinical picture and may escape diagnosis until the reproductive years (76,160,161). Administration of oral contraceptives, which increase the level of factor VIII, can be helpful, and newer therapies, including *desmopressin acetate*, may be necessary, particularly before surgical procedures are performed.

Infectious Causes

Women with cervicitis, particularly chlamydial cervicitis, can experience irregular bleeding and postcoital spotting (see Chapter 16). Therefore, cervical testing for *C. trachomatis* should be considered, especially for adolescents, women in their 20s, and women who are not in a monogamous relationship. Endometritis can cause excessive menstrual flow. Thus, a woman who seeks treatment for menorrhagia and increased menstrual pain and has a history of light-to-moderate previous menstrual flow may have an upper genital tract infection or PID (endometritis, salpingitis, oophoritis). Occasionally, chronic endometritis will be diagnosed when an endometrial biopsy is obtained for evaluation of abnormal bleeding in a patient without specific risk factors for PID.

Neoplasia

Abnormal bleeding is the most frequent symptom of women with invasive cervical cancer. An obvious cervical lesion should be evaluated by biopsy, because the results of cervical cytology testing may be falsely negative with invasive lesions as a result of tumor necrosis. Unopposed estrogen has been associated with a variety of abnormalities of the endometrium, from cystic hyperplasia to adenomatous hyperplasia, hyperplasia with cytologic atypia, and invasive carcinoma. Although vaginal neoplasia is uncommon, the vagina should be evaluated carefully when abnormal bleeding is present. Attention should be directed to all surfaces of the vagina, including anterior and posterior areas that may be obscured by the vaginal speculum on examination.

Diagnosis

For all women, the evaluation of excessive and abnormal menses includes a thorough medical and gynecologic history, the exclusion of pregnancy, the consideration of possible malignancy, and a careful gynecologic examination. For women of normal weight between the ages of approximately 20 and 35 years who do not have clear risk factors for STDs, who have no signs of androgen excess, who are not using exogenous hormones, and who have no other findings on examination, management may be based on a clinical diagnosis. Additional laboratory or imaging studies may be indicated if the diagnosis is not apparent on the basis of examination and history.

Laboratory Studies

In any patients with excessive bleeding, an objective measurement of hematologic status should be performed with a complete blood count to detect anemia or thrombocytopenia. A pregnancy test should be performed to rule out pregnancy-related problems. In addition, because of the possibility of a primary coagulation problem, screening coagulation studies such as a prothrombin time and partial thromboplastin time should be considered; an assessment of platelet function may be appropriate as a screening test for von Willebrand's disease (85).

Imaging Studies

Women with abnormal bleeding who have a history consistent with chronic anovulation, who are obese, or who are older than 35 to 40 years of age require further evaluation. A pelvic ultrasonographic examination may be helpful in delineating anatomic abnormalities if the examination results are suboptimal or if an ovarian mass is suspected. A pelvic ultrasonographic examination is the best technique for evaluating the uterine contour, endometrial thickness, and ovarian structure (162). The use of a vaginal probe transducer allows assessment of endometrial and ovarian disorders, particularly in women who are obese. **Because of variation in endometrial thickness with the menstrual cycle, measurements of endometrial stripe thickness are significantly less useful in premenopausal than postmenopausal women (163).** Sonohysterography is especially helpful in visualizing intrauterine problems such as polyps or submucous leiomyoma (164). Although these sonographic techniques are helpful in visualizing intrauterine pathology, histologic evaluation is required to rule out malignancy (164). Other techniques, such as CT scanning and MRI, are not as helpful in the initial evaluation of causes of abnormal bleeding and should be reserved for specific indications, such as exploring the possibility of other intraabdominal disorders or adenopathy.

Endometrial Sampling

Endometrial sampling should be performed to evaluate abnormal bleeding in women who are at risk for endometrial polyps, hyperplasia, or carcinoma. Such sampling is mandatory in the evaluation of anovulatory bleeding in women older than 35 to 40 years of age, in younger women who are obese, and in those with a history of prolonged anovulation (165). The technique of D & C, which in the past was used extensively for the evaluation of abnormal bleeding, has been replaced largely by endometrial biopsy in the office. The classic study in which a D & C was performed

before hysterectomy with the conclusion that less than one half of the endometrium was sampled in more than one half of the patients has led to questioning the use of D & C for endometrial diagnosis (166,167). Hysteroscopy, either diagnostic or operative, with endometrial sampling, can be performed either in the office or operating room (168).

A number of devices are designed for endometrial sampling (Fig. 14.17), including an inexpensive disposable flexible plastic sheath with an internal plunger that allows tissue aspiration, disposable plastic cannulae of varying diameters that attach to a manually locking syringe that allows the establishment of a vacuum, and cannulae (both rigid metal and plastic) with tissue traps that attach to an electric vacuum pump. Several studies comparing the adequacy of sampling using these devices with D & C have shown a comparable ability to detect abnormalities. It should be noted that these devices are designed to obtain a tissue sample rather than a cytologic washing.

Management

Attention should be directed to establishing a cause of abnormal bleeding. In most cases, medical therapy is effective in managing abnormal bleeding and should be attempted before surgical management. When medical therapy fails in women with anovulatory uterine bleeding who no longer desire future childbearing, endometrial ablation is an efficient and cost-effective alternative to hysterectomy, although this therapy may not be definitive (169). In women with leiomyomas, hysterectomy provides a definitive cure (170). A variety of surgical alternatives to hysterectomy are available to women with symptomatic uterine leiomyomas (171,172).



Figure 14.17 Devices used for sampling endometrium. Top, Metal curette, e.g., Novak (pictured); Bottom, Flexible plastic endometrial sampler, e.g., Pipelle (Unimar), Endocell (pictured) (Wallach Surgical Devices, Inc.).

Nonsurgical Management

Most bleeding problems, including anovulatory bleeding, can be managed nonsurgically (173). Treatment with NSAIDs, such as ibuprofen and mefenamic acid, has been shown to decrease menstrual flow by 30% to 50% (174). Antifibrinolytics such as *tranexamic acid* have been shown to be effective in reducing menstrual blood loss, although this indication is not approved by the U.S. Food and Drug Administration (175,176,177). *Levonorgestrel*-containing intrauterine devices also have been shown to reduce menstrual blood loss significantly and to result in improvements in health-related quality of life that may be comparable to hysterectomy (178,179).

Hormonal management of abnormal bleeding frequently can control excessive or irregular bleeding. The treatment of choice for anovulatory bleeding is medical therapy with oral contraceptives (132). Oral contraceptives have long been used clinically to decrease menstrual flow (88,180,181). Although this effect was first demonstrated with oral contraceptive formulations that contained higher doses of both estrogens and progestins than the agents used today, low-dose combined oral contraceptives have been shown to have a similar effect (182). Low-dose oral contraceptives may be used during the perimenopausal years in healthy nonsmoking women who have no major cardiovascular risk factors. The benefits of menstrual regulation in such women often override the potential risks. The medical treatment

of acute abnormal bleeding in reproductive-age women is the same as that described for adolescents.

For patients in whom estrogen use is contraindicated, progestins, both oral and parenteral, can be used to control excessive bleeding. Cyclic oral *medroxyprogesterone acetate*, administered from days 5 to 26 of the cycle, reduces menstrual flow, although it is less effective than the progestin-containing intrauterine device (179). The benefits of progestins to the patient with oligomenorrhea and anovulation include a regular flow and the prevention of long intervals of amenorrhea, which may end in unpredictable, profuse bleeding. This therapy reduces the risk of hyperplasia resulting from persistent, unopposed estrogen stimulation of the endometrium. Depot formulations of *medroxyprogesterone acetate* also have been used to establish amenorrhea in women at risk of excessive bleeding. Oral, parenteral, or intrauterine delivery of progestins may be used in selected women with atypical endometrial hyperplasia who wish to maintain their fertility (183). Continued monitoring every 3 months is indicated; although the long-term prognosis is uncertain, recurrences are frequent (183). *Danazol* is effective in decreasing bleeding and inducing amenorrhea; it currently is rarely used for ongoing management of abnormal bleeding because of its androgenic side effects, including weight gain, hirsutism, alopecia, and

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irreversible voice changes. Gonadotropin-releasing hormone analogues have also been used for short-term treatment of abnormal bleeding but are not effective for acute therapy given their initial effect as a GnRH agonist (177).

The *levonorgestrel*-containing IUS has been shown to decrease menstrual blood loss by 80% to 90% (184). Because of its 5-year duration of efficacy, it has been suggested as a cost-effective alternative to hysterectomy for excessive bleeding (185).

Surgical Therapy

The surgical management of abnormal bleeding should be reserved for situations in which medical therapy has been unsuccessful or is contraindicated. Although sometimes appropriate as a diagnostic technique, D & C is questionable as a therapeutic modality. One study reported a measured reduction in menstrual blood loss for the first menstrual period only (186). Other studies have suggested a longer-lasting benefit (187).

The surgical options range from a variety of techniques for endometrial ablation or resection (see Chapter 21) to hysterectomy (see Chapter 22) to a variety of conservative surgical techniques for management of uterine leiomyoma, including hysteroscopy with resection of submucous leiomyomas, laparoscopic techniques of myomectomy, uterine artery embolization, and magnetic resonance-

guided focused ultrasonography ablation. The choice of procedure depends on the cause of the bleeding, the patient's preferences, the physician's experience and skills, the availability of newer technologies, and a careful assessment of risks versus benefits based on the patient's medical condition, concomitant gynecologic symptoms or conditions, and desires for future fertility. The assessment of the relative advantages, risks, benefits, complications, and indications of these procedures is a subject of ongoing clinical research (188,189). The proposed advantages of techniques other than hysterectomy include a shorter recovery time and less early morbidity. However, symptoms can recur or persist; repeat procedures or subsequent hysterectomy may be required if conservative options are chosen. Quality-of-life outcomes should be assessed, and current studies do not indicate there is a definitive management advantage to any particular technique (190,191,192). Much has been written about the psychologic sequelae of hysterectomy, and some of the aforementioned surgical techniques have been developed in an effort to provide less drastic management options. **Most well-controlled recent studies have suggested that, in the absence of preexisting psychopathology, indicated but elective surgical procedures for hysterectomy have few, if any, significant psychologic sequelae (including depression)** (193) (see Chapter 12).

Pelvic Masses

Conditions diagnosed as a pelvic mass in women of reproductive age are presented in Table 14.7.

Differential Diagnosis

It is difficult to determine the frequency of diagnoses of pelvic mass in women of reproductive age, because many pelvic masses are not ultimately treated with surgery. **Nonovarian or nongynecologic conditions may be confused with an ovarian or uterine mass** (Table 14.8). The frequency of masses found at laparotomy has been studied, although the percentages are affected by varying indications for surgery, indications for referral, type of practice (gynecologic oncology versus general gynecology), and patient populations (a higher percentage of African-Americans with uterine leiomyomas, for example). Benign masses, such as functional ovarian cysts or asymptomatic uterine leiomyoma, often do not require surgery.

Age is an important determinant of the likelihood of malignancy. In one study of women who underwent laparotomy for pelvic mass, malignancy was seen in only 10% of those younger than 30 years of age, and most of these tumors had low malignant potential (194). **The most common tumors found during laparotomy for pelvic mass are mature cystic teratomas or dermoids (seen in one third of women**

younger than 30 years of age) and endometriomas (approximately one fourth of women 31 to 49 years of age) (194).

Table 14.7 Conditions Diagnosed as a Pelvic Mass in Women of Reproductive Age
<i>Full urinary bladder</i>
<i>Urachal cyst</i>
<i>Sharply anteflexed or retroflexed uterus</i>
<i>Pregnancy (with or without concomitant leiomyomas)</i>
Intrauterine
Tubal
Abdominal
<i>Ovarian or adnexal masses</i>
Functional cysts
Inflammatory masses
Tubo-ovarian complex
Diverticular abscess
Appendiceal abscess
Matted bowel and omentum
Peritoneal cyst
Stool in sigmoid
Neoplastic tumors
Benign
Malignant
<i>Paraovarian or paratubal cysts</i>
<i>Intraligamentous myomas</i>
<i>Less common conditions that must be excluded:</i>
Pelvic kidney
Carcinoma of the colon, rectum, appendix
Carcinoma of the fallopian tube
Retroperitoneal tumors (anterior sacral meningocele)
Uterine sarcoma or other malignant tumors

Table 14.8 Ultrasonographic Characteristics of Adnexal Masses That May Be Useful In Predicting Malignancy

Unilocular cyst vs. multilocular vs. solid components
Regular contour vs. irregular border
Smooth walls vs. nodular vs. irregular
Presence or absence of ascites
Unilateral vs. bilateral
Wall thickness
Internal echogenicity
Presence of other intra-abdominal pathology (liver, etc.)
Vascular characteristics and color flow Doppler pattern

Uterine Masses

Uterine leiomyomas, most of which are asymptomatic, are by far the most common benign uterine tumors (195). Other benign uterine growths, such as uterine vascular tumors, are rare. Uterine leiomyomas may be diagnosed on physical examination or with pelvic imaging. They may be subserosal, intramucosal, or submucosal in location within the uterus or located in the cervix, in the broad ligament, or on a pedicle (Fig. 14.18). They are estimated to be present in a high percentage of all women of reproductive age and may be discovered incidentally during routine annual examination. **Asymptomatic fibroids may be present in 40% to 50% of women older than 35 years of age** (155). **Using ultrasonography screening, other authors have estimated a cumulative incidence by age 50 of greater than 80% in African-American women and nearly 70% in white women** (153). Leiomyomas may occur singly but often are multiple. They may cause a range of symptoms, from abnormal bleeding to pelvic pressure; however, fewer than one half of uterine leiomyomas are estimated to produce symptoms (196).

The cause of uterine leiomyomas is unknown. Several studies have suggested that each leiomyoma arises from a single neoplastic cell within the smooth muscle of the myometrium (197). There appears to be an increased familial incidence, and they may be more common in women who are obese (155). Hormonal responsiveness and binding has been demonstrated *in vitro*. Fibroids have the potential to enlarge during pregnancy as well as to regress

after menopause.

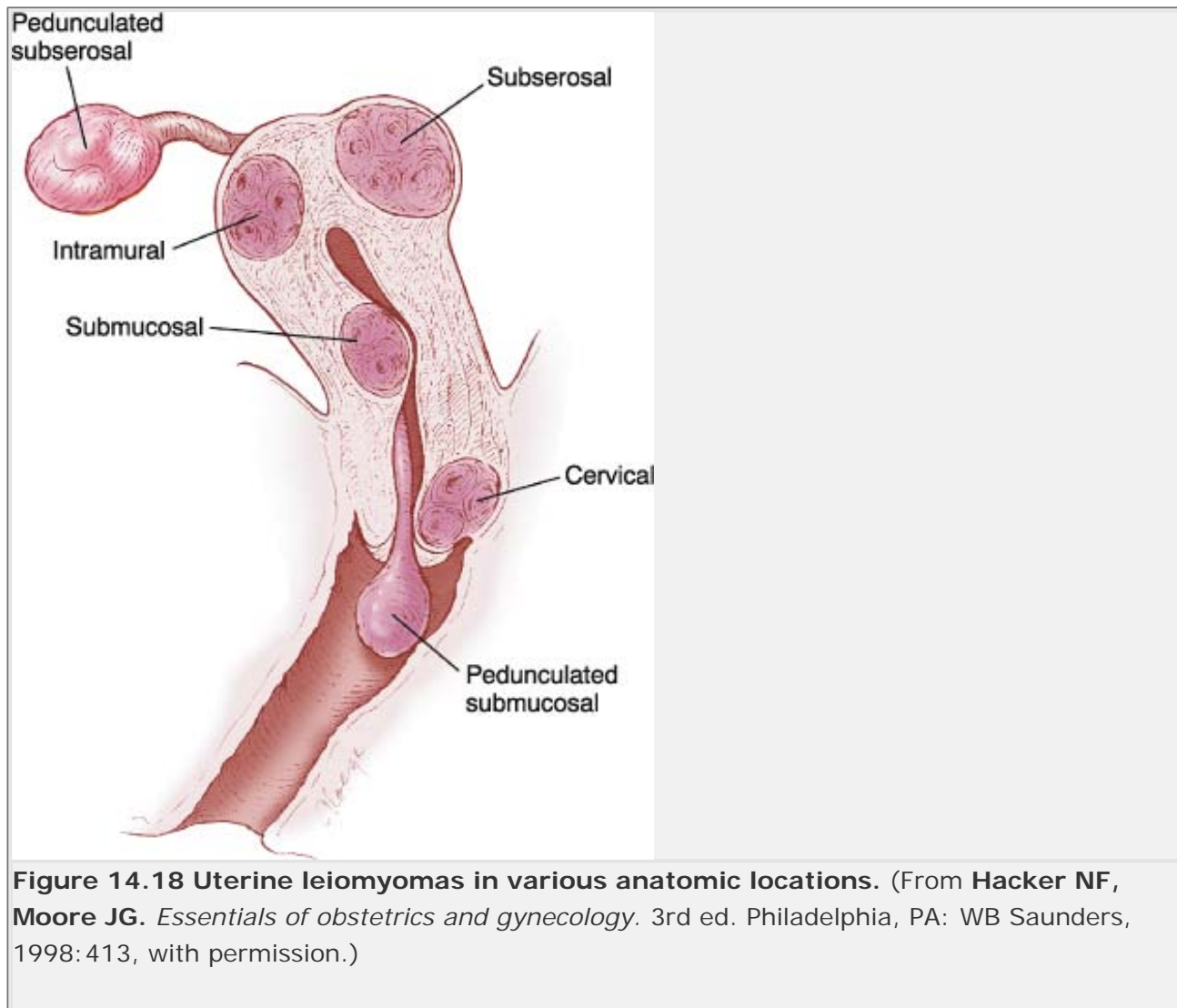


Figure 14.18 Uterine leiomyomas in various anatomic locations. (From Hacker NF, Moore JG. *Essentials of obstetrics and gynecology*. 3rd ed. Philadelphia, PA: WB Saunders, 1998: 413, with permission.)

Grossly, fibroids are discrete nodular tumors that vary in size and number (Fig. 14.18). They may be microscopic or huge (a uterine weight of 74 lb has been reported). They may cause symmetric uterine enlargement or they may distort the uterine contour significantly. The consistency of an individual leiomyoma varies from hard and stony (as with a calcified leiomyoma) to soft (as with cystic degeneration), although the usual consistency is described as firm or rubbery. Although they do not have a true capsule, the margins of the tumor are

blunt, noninfiltrating, and pushing, and are usually separated from the myometrium by a pseudocapsule of connective tissue, which allows easy enucleation at the time of surgery. There is usually one major blood vessel supplying each tumor. The cut surface is characteristically whorled.

Degenerative changes are reported in approximately two thirds of all surgical specimens (198). Leiomyomas with an increased number of mitotic figures may occur in various forms: in women who are pregnant or taking progestational agents, with necrosis, and as a **smooth muscle tumor of uncertain malignant potential (defined as having 5 to 9 mitoses per 10 high-power fields [hpf] that do not demonstrate nuclear atypia or giant cells, or with a lower mitotic count [2–4 mitoses/10 hpf] that does demonstrate atypical nuclear features or giant cells)**. Studies suggest that “malignant degeneration” of a preexisting leiomyoma is extremely uncommon (199).

Leiomyosarcoma is a rare malignant neoplasm composed of cells that have smooth muscle differentiation (see Chapter 33); cytogenetic studies suggest that they arrive *de novo* via distinct pathogenetic pathways (200). The typical patient with leiomyosarcoma is in her mid-50s and seeks treatment for abnormal bleeding. In most cases, diagnoses are determined (postoperatively) after microscopic examination of a uterus removed because of suspected leiomyomas. **Sarcomas that have a malignant behavior have 10 mitoses/hpf or greater.**

Uterine leiomyomas are frequently diagnosed on the basis of clinical findings of an enlarged, irregular uterus on pelvic examination. They are also frequently noted on ultrasonography obtained for a variety of indications and may be an incidental finding. However, any pelvic tumor potentially can be confused with an enlarged uterus.

The most common initial symptom associated with fibroids, and the one that most frequently leads to surgical intervention, is menorrhagia. Chronic pelvic pain may also be present. Pain may be characterized as dysmenorrhea, dyspareunia, or pelvic pressure (see Chapter 15). Acute pain may result from torsion of a pedunculated leiomyoma or infarction and degeneration. The following urinary symptoms may be present:

- Frequency may result from extrinsic pressure on the bladder.
- Partial ureteral obstruction may be caused by pressure from large tumors at the pelvic brim. Reports suggest some degree of ureteral obstruction in 30% to 70% of tumors above the pelvic brim. Ureteral compression is three to four times more common on the right, because the left ureter is protected by the sigmoid colon.

- Rarely, complete urethral obstruction results from elevation of the base of the bladder by the cervical or lower uterine leiomyoma with impingement on the region of the internal sphincter.

Leiomyomas are an infrequent primary cause of infertility and have been reported as a sole cause in only a small percentage of infertile patients (201,202). Pregnancy loss or complications such as preterm labor, intrauterine growth restriction, and malpresentation can occur in women with leiomyomas, although most patients have uncomplicated pregnancies and deliveries (201). One study calculated a 10% rate of pregnancy complications in women with fibroids (203). **Although growth of leiomyomas may occur with pregnancy, no demonstrable change in size (based on serial ultrasonographic examination)**

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has been noted in 70% to 80% of patients (204,205). The risk of pregnancy complications is influenced by both myoma location and size (206).

The following symptoms may infrequently be associated with leiomyomas:

- Rectosigmoid compression, with constipation or intestinal obstruction
- Prolapse of a pedunculated submucous tumor through the cervix, with associated symptoms of severe cramping and subsequent ulceration and infection (uterine inversion also can occur)
- Venous stasis of the lower extremities and possible thrombophlebitis secondary to pelvic compression
- Polycythemia
- Ascites

Ovarian Masses

During the reproductive years, the most common ovarian masses are benign. Ovarian masses can be functional or neoplastic, and neoplastic tumors can be benign or malignant.

Functional ovarian masses include follicular and corpus luteal cysts. About two thirds of

85%) are benign, and two thirds of these occur in women between 20 and 44 years of age.

The chance that a primary ovarian tumor is malignant in a patient younger than 45 years of age is less than 1 in 15. Most tumors produce few or only mild, nonspecific

symptoms. The most common symptoms include abdominal distension, abdominal pain or discomfort, lower abdominal pressure sensation, and urinary or gastrointestinal symptoms. If the tumor is hormonally active, symptoms of hormonal imbalance, such as vaginal bleeding related to estrogen production, may be present. Acute pain may occur with adnexal torsion, cyst rupture, or bleeding into a cyst. Pelvic findings in patients with benign and malignant tumors may differ. Masses that are unilateral, cystic, mobile, and smooth are most likely to be benign, whereas those that are bilateral, solid, fixed, irregular, and associated with ascites, *cul-de-sac* nodules, and a rapid rate of growth are more likely to be malignant.

In assessing ovarian masses, the distribution of primary ovarian neoplasms by decade of life can be helpful (207). Ovarian masses in women of reproductive age are most likely to be benign, but the possibility of malignancy must be considered (208) (Fig. 14.19).

Nonneoplastic Ovarian Masses

Functional ovarian cysts include follicular cysts, corpus luteum cysts, and theca lutein cysts. All are benign and usually do not cause symptoms or require

surgical management. Cigarette smoking has been associated with an increased risk of functional cysts (209). Oral contraceptive use has been associated with a decreased risk (210). The annual rate of hospitalization for functional ovarian cysts has been estimated to be as high as 500 per 100,000 woman-years in the United States, although little is known about the epidemiology of the condition (211). **The most common functional cyst is the follicular cyst, which is rarely larger than 8 cm.** A cystic follicle can be defined as a follicular cyst when its diameter is greater than 3 cm. These cysts are usually found incidental to pelvic examination, although they may rupture, causing pain and peritoneal signs. They usually resolve in 4 to 8 weeks with expectant management (212).

Corpus luteum cysts are less common than follicular cysts. Corpus luteum cysts may rupture, leading to a hemoperitoneum and requiring surgical management. Patients taking anticoagulant therapy are at particular risk for rupture. Rupture of these cysts occurs more often on the right side and may occur during intercourse. **Most ruptures occur on cycle days 20 to 26** (213). Unruptured corpus luteum cysts can cause pain, presumably because of bleeding into the enclosed ovarian cyst cavity. They can produce symptoms that can be difficult to discern from adnexal torsion.

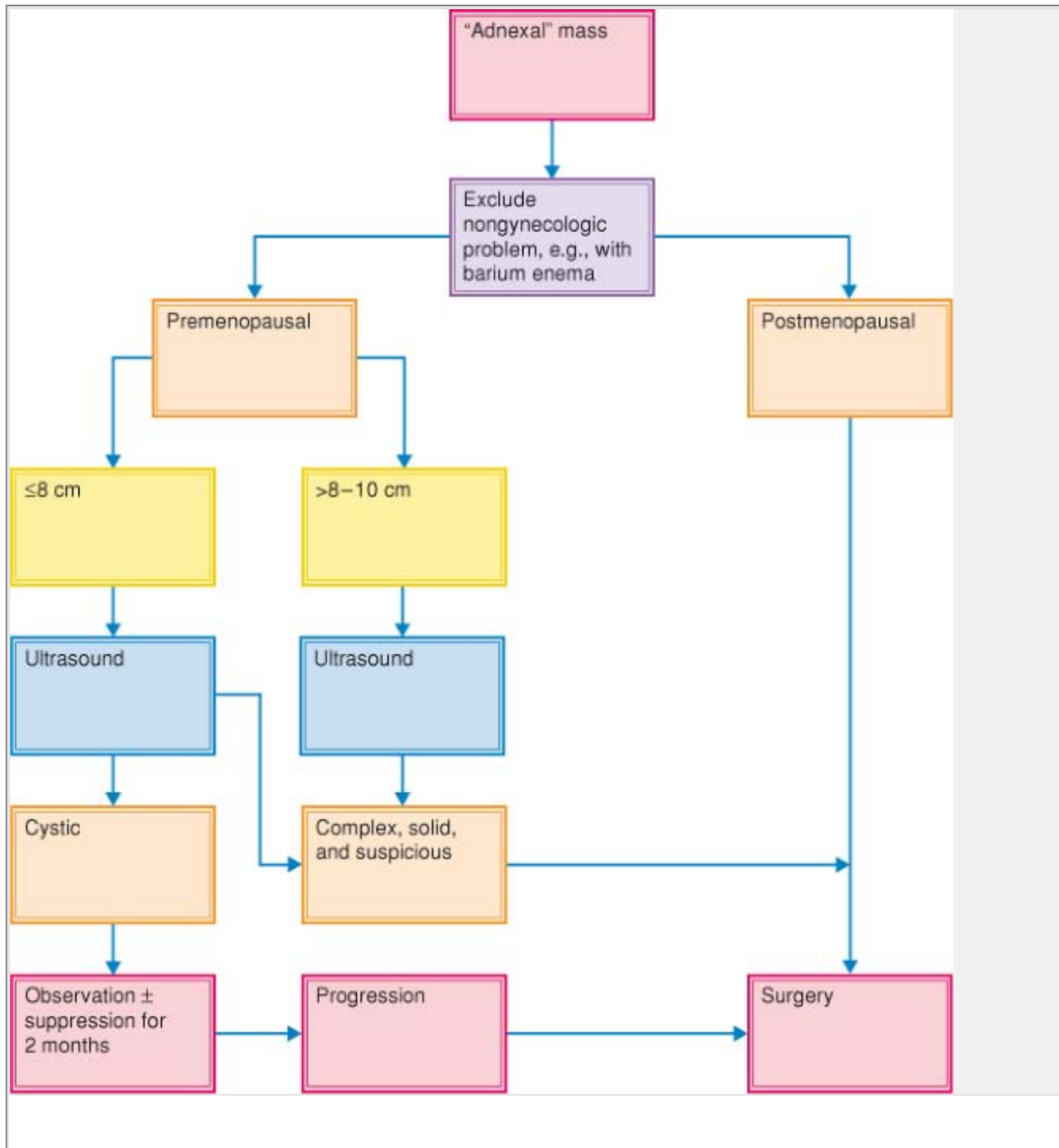


Figure 14.19 Preoperative evaluation of the patient with an adnexal mass. (From Berek JS, Hacker NF. *Practical gynecologic oncology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005: 465.)

Theca lutein cysts are the least common of functional ovarian cysts. They are usually bilateral and occur with pregnancy, including molar pregnancies. They may be associated with multiple gestations, molar pregnancies, choriocarcinoma, diabetes, Rh sensitization, clomiphene citrate use, human menopausal gonadotropin–human chorionic gonadotropin ovulation induction, and the use of GnRH analogs. Theca lutein cysts may be quite large (up to 30 cm), are multicystic, and regress spontaneously (214,215).

Combination monophasic oral contraceptive therapy has been reported to markedly reduce the risk of functional ovarian cysts (216). It appears that, in comparison with previously available higher-dose pills, the effect of cyst suppression with current low-dose oral contraceptives is attenuated (217,218). Most studies have suggested that the use of

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triphasic oral contraceptives is not associated with an appreciable increased risk of functional ovarian cysts (219).

Other Benign Masses

Women with endometriosis may develop ovarian endometriomas (“chocolate” cysts), which can enlarge to 6 to 8 cm in size. A mass that does not resolve with observation may be an endometrioma (see Chapter 29).

Although enlarged, polycystic ovaries were originally considered the *sine qua non* of PCOS. They probably represent a final common phenotype of a wide variety of causes and are not always present with other features of the syndrome. The prevalence of PCOS among the general population depends on the diagnostic criteria used. In one study, 257 volunteers were examined with ultrasonography; 22% were found to have polycystic ovaries (220). The finding of bilaterally enlarged ovaries on examination or polycystic ovaries on ultrasonographic examination should prompt evaluation for the full-blown syndrome, which includes hyperandrogenism and chronic anovulation as well as polycystic ovaries (150,221). Therapy for PCOS is medical and generally not surgical.

Neoplastic Masses

More than 80% of benign cystic teratomas (dermoid cysts) occur during the

reproductive years, although dermoid cysts have a wider age distribution than other ovarian germ cell tumors (Fig. 14.20) (222). Histologically, benign cystic teratomas have an admixture of elements. In one study of ovarian masses that were surgically excised, dermoid cysts represented 62% of all ovarian neoplasms in women younger than 40 years of age (207). Malignant transformation occurs in less than 2% of dermoid cysts in women of all ages; most cases occur in women older than 40 years of age. The risk of torsion with dermoid cysts is approximately 15%, and it occurs more frequently than with ovarian tumors in general, perhaps because of the high-fat content of most dermoid cysts, allowing them to float within the abdominal and pelvic cavity. As a result of this fat content, on pelvic examination a dermoid cyst frequently is described as anterior in location. They are bilateral in approximately 10% of cases, although many have advanced the argument against bivalving a normal-appearing contralateral ovary because of the risk of adhesions, which may result in infertility. **An ovarian cystectomy is almost always possible, even if it appears that only a small amount of ovarian tissue remains.** Preserving a small amount of ovarian cortex in a young patient with a benign lesion is preferable to the loss of the entire ovary (223). Laparoscopic cystectomy often is possible, and intraoperative spill of tumor contents is rarely a cause of complications (224,225).

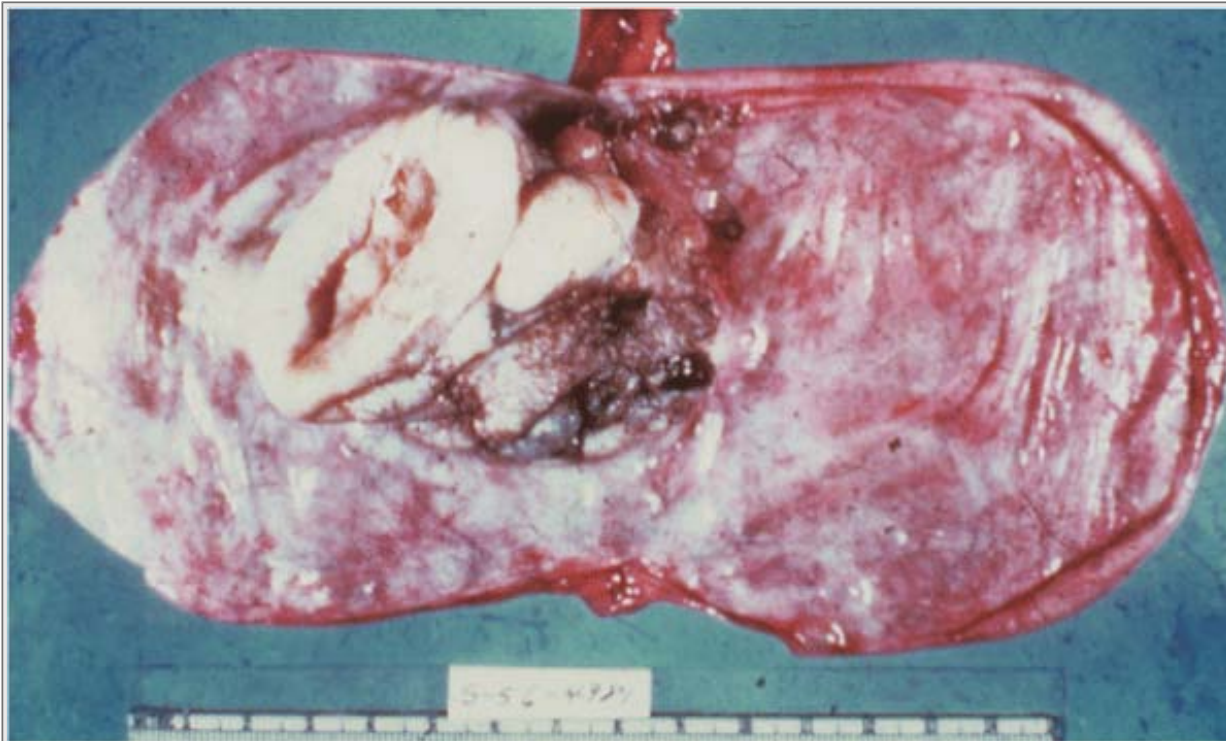
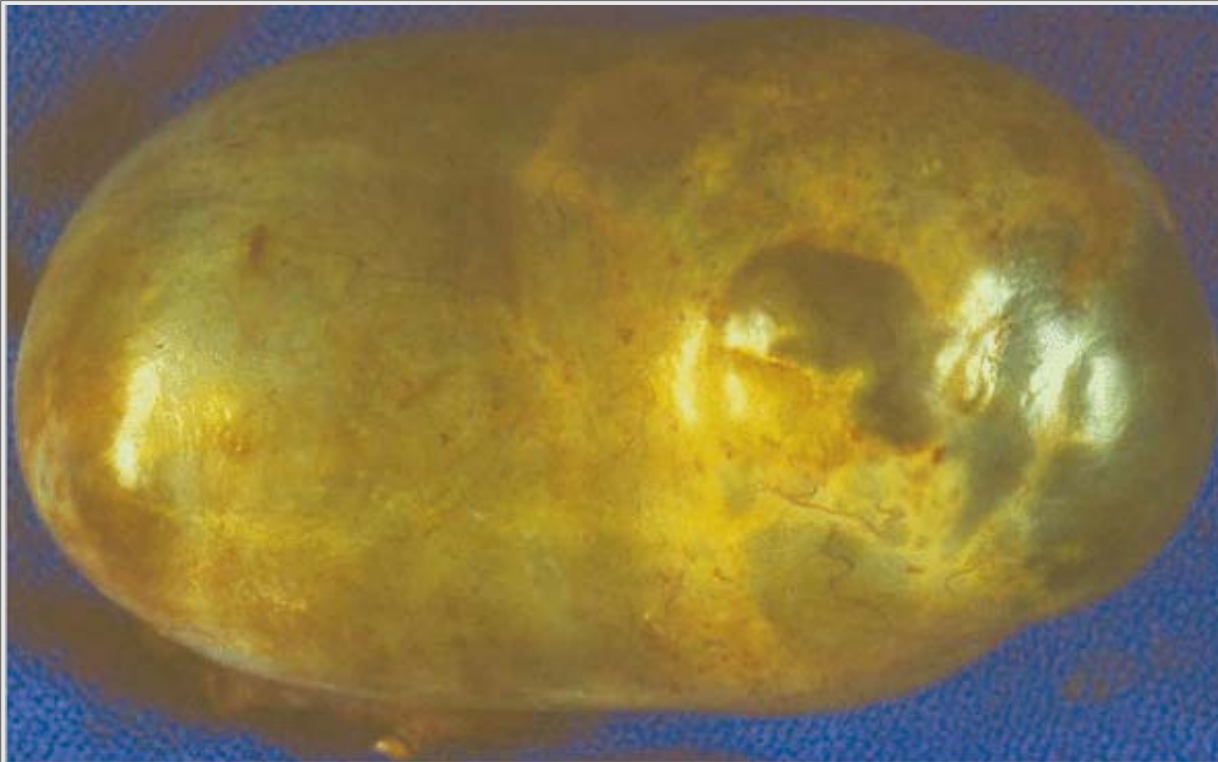


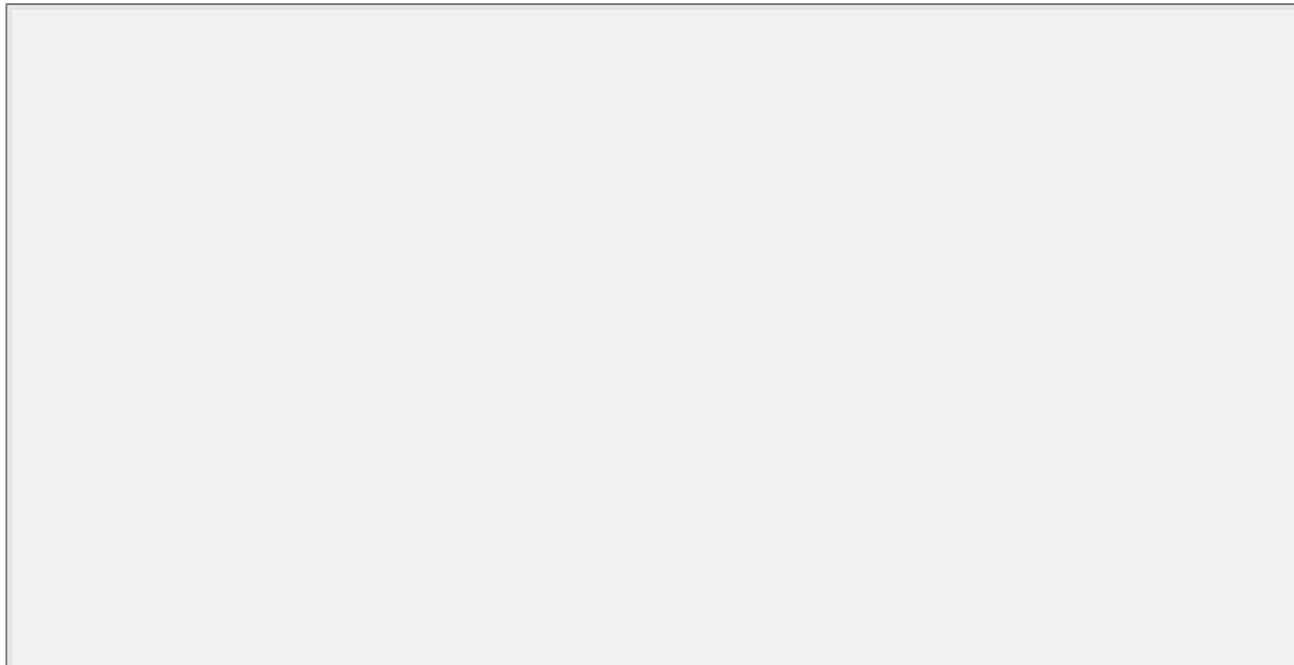
Figure 14.20 Mature cystic teratoma (dermoid cyst) of the ovary.**Figure 14.21 Mucinous cystadenoma.**

The risk of epithelial tumors increases with age. Although serous cystadenomas are often considered the more common benign neoplasm, in one study, benign cystic teratomas represented 66% of benign tumors in women younger than 50 years of age; serous tumors accounted for only 20% (207). **Serous tumors are generally benign; 5% to 10% have borderline malignant potential, and 20% to 25% are malignant.** Serous cystadenomas are often multilocular, sometimes with papillary components. The surface epithelial cells secrete serous fluid, resulting in a watery cyst content. Psammoma bodies, which are areas of fine calcific granulation, may be scattered within the tumor and are visible on radiograph. A frozen section is necessary to distinguish between benign, borderline, and malignant serous tumors because this distinction cannot be made on gross examination alone. Mucinous ovarian tumors may grow to large dimensions. Benign mucinous tumors

typically have a lobulated, smooth surface, are multilocular, and may be bilateral in up to 10% of cases. Mucoïd material is present within the cystic loculations (Fig. 14.21). **Five to ten percent of mucinous ovarian tumors are malignant.** They may be difficult to distinguish histologically from metastatic gastrointestinal malignancies. Other benign ovarian tumors include fibromas (a focus of stromal cells), Brenner tumors (which appear grossly similar to fibromas and which are frequently found incidentally), and mixed forms of tumors, such as the cystadenofibroma (Fig. 14.22).

Other Adnexal Masses

Masses that include the fallopian tube are related primarily to inflammatory causes in the reproductive age group. A tubo-ovarian abscess can be present in association with PID (see Chapter 16). In addition, a complex inflammatory mass consisting of bowel, tube, and ovary may be present without a large abscess cavity. Ectopic pregnancies can occur in the reproductive age group and must be excluded when a patient presents with pain, a positive pregnancy test, and an adnexal mass (see Chapter 18). Paraovarian cysts may be noted either on examination or on imaging studies. In many instances, a normal ipsilateral ovary can be visualized using ultrasonography. The frequency of malignancy in paraovarian tumors is quite low and may be more common in paraovarian masses larger than 5 cm (225,226).



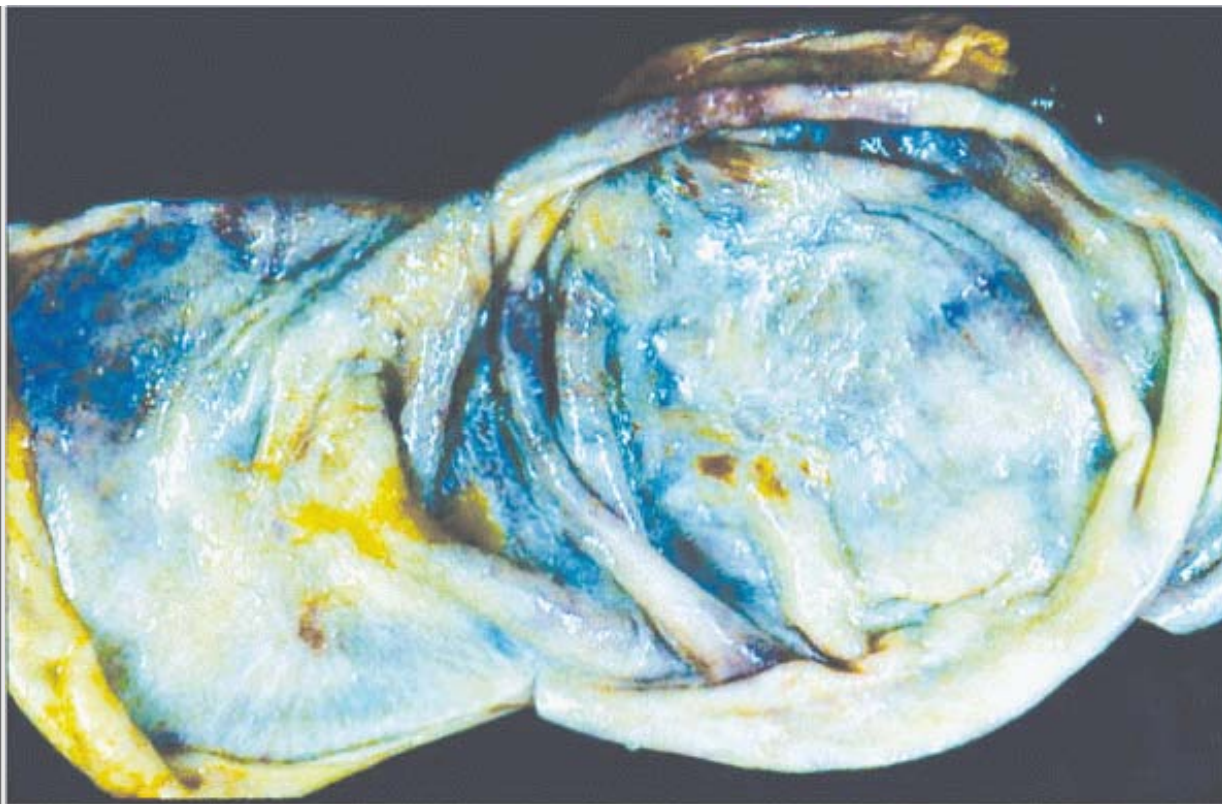


Figure 14.22 Mucinous cystadenofibroma.

Diagnosis

A complete pelvic examination, including rectovaginal examination and Pap test, should be performed. **Estimations of the size of a mass should be presented in centimeters** rather than in comparison to common objects or fruit (e.g., orange, grapefruit, tennis ball, golf ball). After pregnancy has been excluded, one simple office technique that can help determine whether a mass is uterine or adnexal includes sounding and measuring the depth of the uterine cavity. Diagnosis of uterine leiomyomas usually is based on the characteristic finding of an irregularly enlarged uterus. The size and location of the usually multiple leiomyomas can be confirmed and documented with pelvic ultrasonography (Fig. 14.23). If the examination is adequate to confirm uterine leiomyoma and symptoms are absent, ultrasonography is not always necessary unless an ovarian mass cannot be excluded.

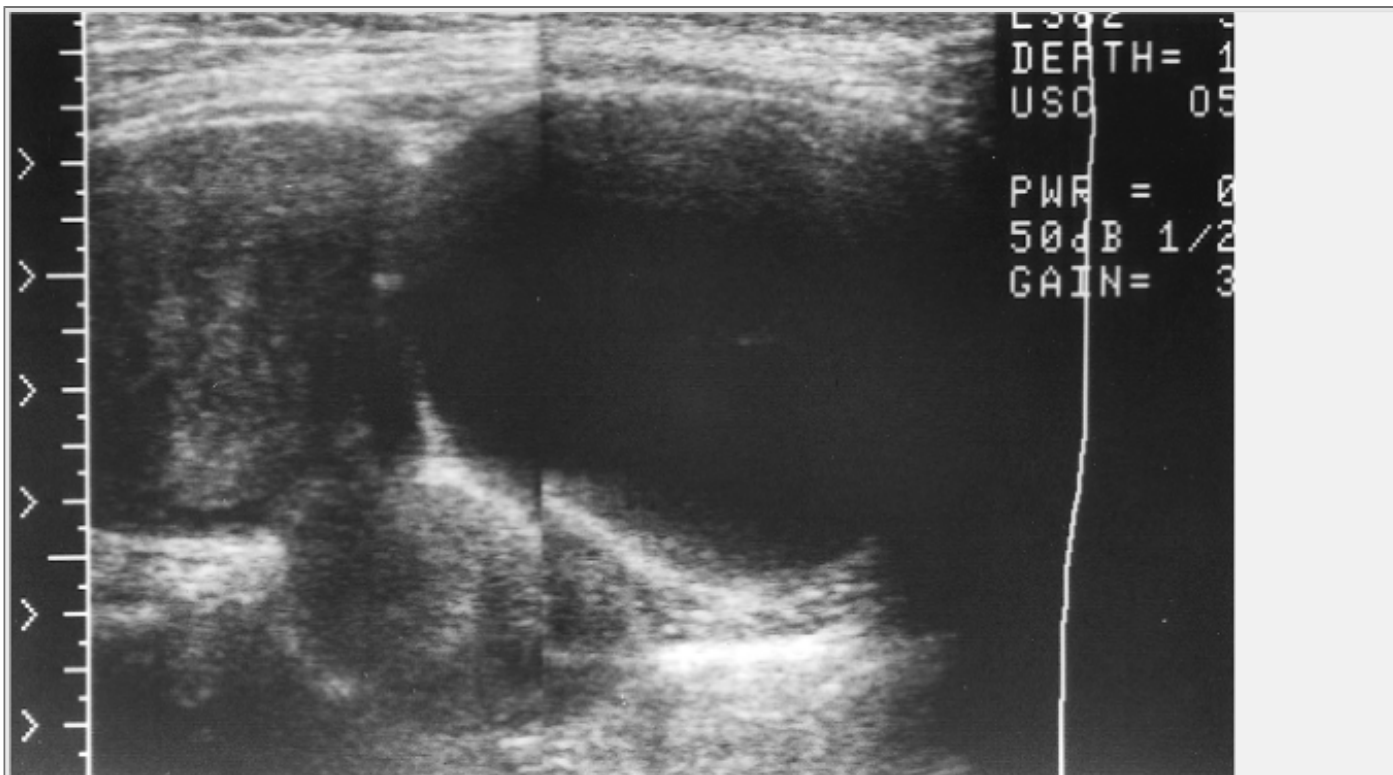


Figure 14.23 Transvaginal pelvic ultrasound demonstrating multiple uterine leiomyomas.

Other Studies

Endometrial sampling with an endometrial biopsy or D & C is mandatory when both pelvic mass and abnormal bleeding are present. An endometrial lesion—carcinoma or hyperplasia—may coexist with a benign mass such as a leiomyoma. In a woman with leiomyomas, abnormal bleeding cannot be assumed to be caused solely by the fibroids. Clinicians differ in recommendations about the need for endometrial biopsy when the diagnosis is leiomyomas with regular menses.

If urinary symptoms are prominent, studies of the urinary tract may be necessary, including cystometric measurements if incontinence or pressure are present. Cystoscopy may sometimes be necessary or appropriate to rule out intrinsic bladder lesions.

Laboratory Studies

Laboratory studies that are indicated for women of reproductive age with a pelvic mass include pregnancy test, cervical cytology, complete blood count, erythrocyte sedimentation rate, and testing of stool for occult blood. The value of tumor markers, such as CA125 in a premenopausal woman with a pelvic mass, has been widely debated. **A number of benign conditions, including uterine leiomyomas, PID, pregnancy, and endometriosis can cause elevated CA125 levels; thus, measurement of CA125 levels is not useful in most circumstances because it may lead to unnecessary surgical intervention.**

Imaging Studies

Other studies may be necessary or appropriate. The most commonly indicated study is pelvic ultrasonography, which will help document the origin of the mass to determine whether it is uterine, adnexal, bowel, or gastrointestinal. The ultrasonographic examination also provides information about the size of the mass and its consistency—unilocular cyst, mixed echogenicity (Fig. 14.24), multiloculated cyst, solid mass (Fig. 14.25)—which can help determine management.

The value of transvaginal and transabdominal ultrasonography in the diagnosis of pelvic masses has been compared. Transvaginal ultrasonography has the advantage of providing additional information about the internal architecture or anatomy of the mass. Heterogeneous pelvic masses, described as tub-ovarian abscesses on transabdominal ultrasonography, can with transvaginal ultrasonography be differentiated as pyosalpinx, hydrosalpinx, tubo-ovarian complex, and tubo-ovarian abscess (101) (Fig. 14.26).

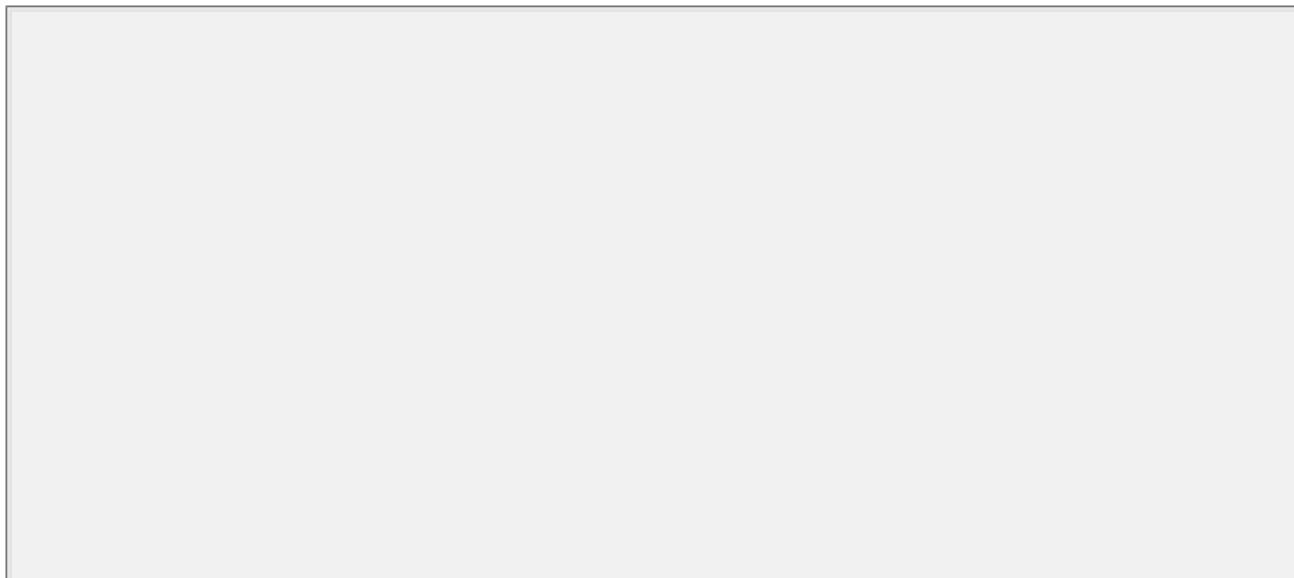




Figure 14.24 Transvaginal ultrasonogram of a unilocular ovarian cyst. This is characteristic of a benign process or corpus luteum cyst.

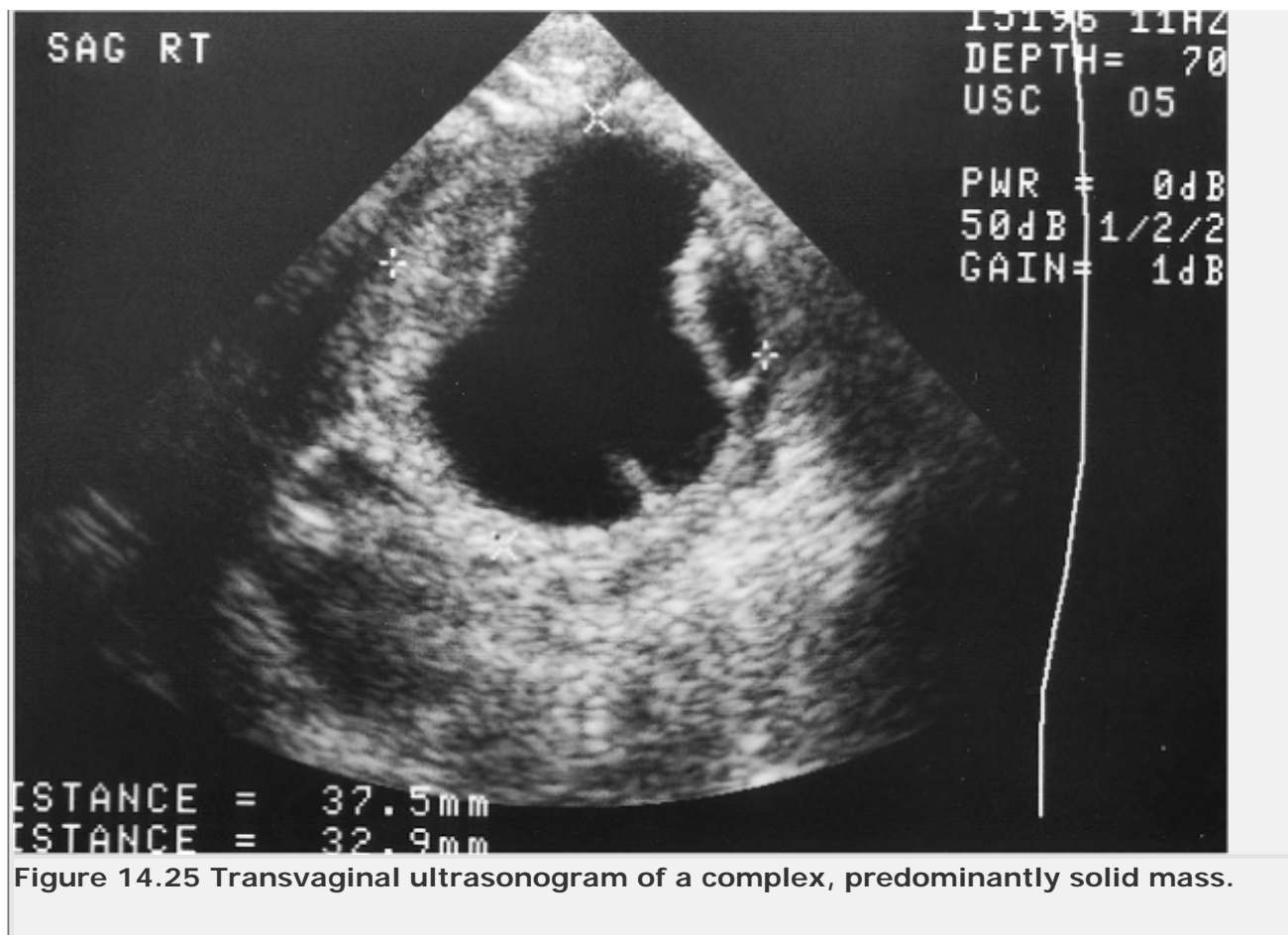


Figure 14.25 Transvaginal ultrasonogram of a complex, predominantly solid mass.

The diagnostic accuracy of transvaginal ultrasonography in diagnosing endometrioma can be quite high (Fig. 14.27). Endometriomas can have a variety of ultrasonographic appearances, from purely cystic, to varying degrees of complexity with septation or debris, to a solid appearance. A variety of scoring systems have been developed with the intent of predicting benign versus malignant adnexal masses; the ultrasonographic characteristics used in many types of scoring systems are listed in Table 14.8 (227,228,229). Risk of malignancy indices have been developed that use ultrasound characteristics in conjunction with menopausal status and CA125 values in an attempt to predict the risk of malignancy in ovarian masses (230,231,232). Although an analysis of such features may be helpful, histologic confirmation of surgically removed persistent masses remains the standard of care (233).



Figure 14.26 Transvaginal ultrasonogram of bilateral tubo-ovarian abscesses.

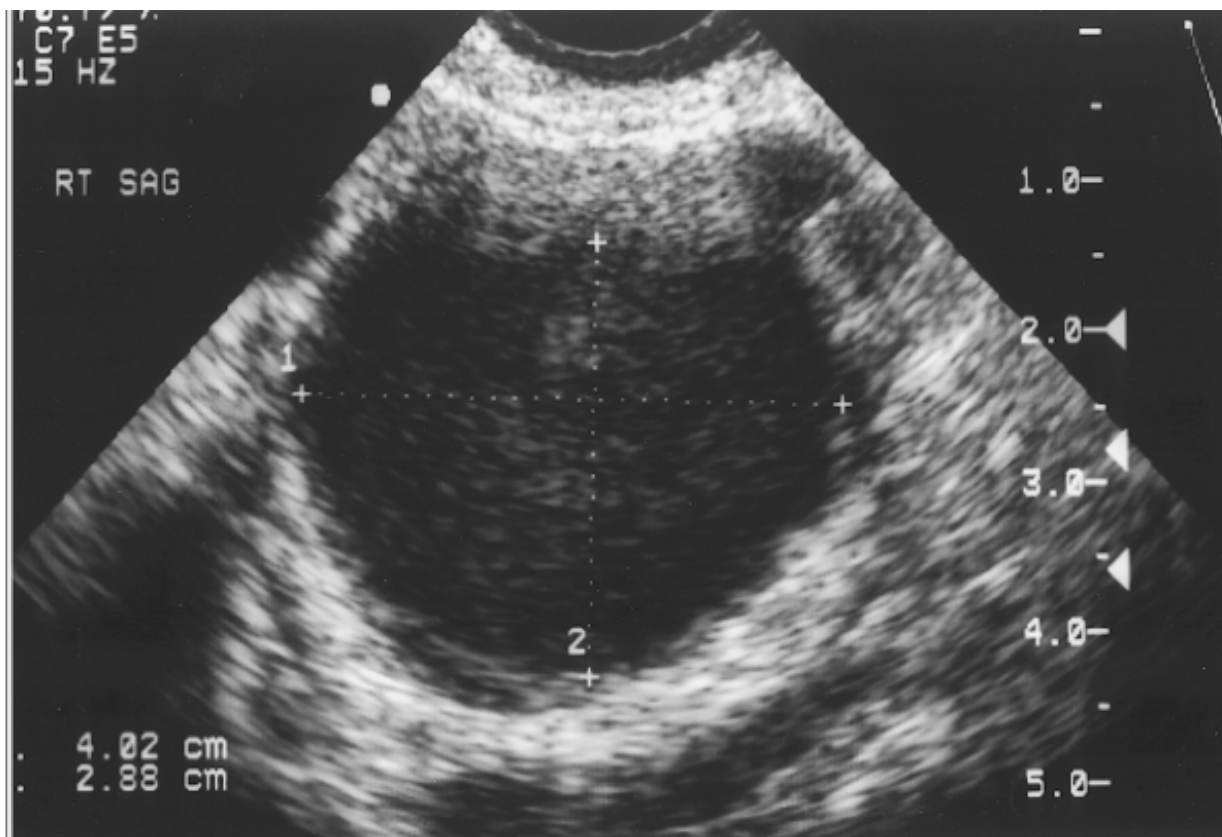


Figure 14.27 Transvaginal ultrasonogram of an endometrioma of the ovary.

Computed tomography seldom is indicated as a primary diagnostic procedure, although it may be helpful in planning treatment when a malignancy is strongly suspected or when a nongynecologic disorder may be present. Abdominal flat-plate radiography is not a primary diagnostic procedure, although if used for other indications, it may reveal calcifications that can assist in the discovery or diagnosis of a mass. Pelvic calcifications (teeth) consistent with a benign cystic teratoma (Fig. 14.28), a calcified uterine fibroid, or scattered calcifications consistent with psammoma bodies of a papillary serous cystadenoma can be seen with abdominal radiography.

Ultrasonography, CT imaging, or an intravenous pyelography may be appropriate to demonstrate ureteral deviation, compression, or dilation in the presence of moderately large and laterally located fibroids or other pelvic mass. Such findings rarely provide an indication for surgical intervention for otherwise asymptomatic leiomyomas.

Hysteroscopy provides direct evidence of intrauterine pathology or submucous leiomyomas that distort the uterine cavity (see Chapter

21). Hysterosalpingography will demonstrate indirectly the contour of the endometrial cavity and any distortion or obstruction of the uterotubal junction secondary to leiomyomas, an extrinsic mass, or peritubal adhesions. The techniques combining hysterosalpingography, in which fluid is instilled into the uterine cavity, with transvaginal ultrasonography have been helpful in the diagnosis of intrauterine pathology. Hysterosalpingography or sonohysterography may be indicated in women with infertility and uterine leiomyoma (195).

Magnetic resonance imaging may be most useful in the diagnosis of uterine anomalies, although its value rarely justifies the increased cost of the procedure over ultrasonography for the diagnosis of other pelvic masses (234,235,236).



Figure 14.28 Benign cystic teratoma (dermoid cyst) of the ovary with teeth seen on abdominal radiograph.

Management

The management of a pelvic mass is based on an accurate diagnosis. An explanation of this diagnosis should be conveyed to the patient, along with a discussion of the likely course of the disease (e.g., growth of uterine leiomyomas, regression of fibroids at menopause, regression of a follicular cyst, the uncertain malignant potential of an ovarian mass). All options for management should be presented and discussed, although it is appropriate for the physician to state a recommended approach with an explanation of the reasons for the recommendation. Management should be based on the primary symptoms and may include observation with close follow-up, temporizing surgical therapies, medical management, or definitive surgical procedures.

Leiomyomas

The management of uterine leiomyomas is dependent on the patient's age and proximity to anticipated menopause, symptoms, patient preference, and the experience and skills of the clinician. Variability in reporting data regarding severity of symptoms, uterine anatomy, and response to therapy make it difficult to compare different types of therapies, which include observation, medical, surgical, and radiologic-based techniques difficult (151,237).

Nonsurgical Management

Judicious patient observation and follow-up are indicated primarily for uterine leiomyomas; intervention is reserved for specific indications and symptoms (171). Periodic examinations are indicated to ensure that the tumors are not growing rapidly. Uterine size should be recorded on the patient's chart, and the location of palpable and ultrasonographically localized leiomyomas should be described and diagramed.

The use of GnRH agonists results in a 40% to 60% decrease in uterine volume and can be of value in some clinical situations. Treatment results in hypoestrogenism, which has been associated with reversible bone loss and symptoms such as hot flashes. Thus, treatment has been limited to short-term use, although low-dose hormonal therapy may be effective in

minimizing the hypoestrogenic effects. Regrowth of leiomyomas is experienced within a few months after stopping therapy in about one half of women treated. Some indications for the use of GnRH agonists in women with leiomyomas are as follows:

- Preservation of fertility in women with large leiomyomas before attempting conception or preoperative treatment before myomectomy
- Treatment of anemia to allow recovery of normal hemoglobin levels before surgical management, minimizing the need for transfusion or allowing autologous blood donation
- Treatment of women approaching menopause in an effort to avoid surgery
- Preoperative treatment of large leiomyomas to make vaginal hysterectomy, hysteroscopic resection or ablation, or laparoscopic destruction more feasible
- Treatment of women with medical contraindications to surgery
- Treatment of women with personal or medical indications for delaying surgery

Therapies combining GnRH agonists with estrogen add-back therapy (estrogen–progestin, progestin alone, and recently tibolone) have shown promise in reducing side effects of agonist therapy alone, although this therapy is a costly alternative (238,239). *Tibolone*, a synthetic steroid with estrogenic, progestational, and androgenic activity, has been widely used outside the United States for treatment of menopausal symptoms; its use with GnRH agonists as add-back therapy holds promise for longer-term therapy of leiomyoma (240). Selective estrogen or progesterone receptor modulators, GnRH antagonists, antiprogestins such as *mifepristone*, and other nonhormonal medications hold promise for future therapy and are under investigation (241,272,243). As the role of growth factors in leiomyoma-associated bleeding is better elucidated, treatment targeted at the growth factor or its receptor may prove useful. In addition, as the molecular biology and genetics of leiomyoma are better understood, newer nonsurgical therapies may be developed.

Surgical Therapy

Determining potential indications for surgical treatment requires careful judgment and assessment of the degree of associated symptoms. **Asymptomatic leiomyomas do not usually require surgery.** Potential indications for surgery include the following:

- Abnormal uterine bleeding with resultant anemia, unresponsive to hormonal or other conservative management
- Chronic pain with severe dysmenorrhea, dyspareunia, or lower abdominal pressure or pain
- Acute pain, as in torsion of a pedunculated leiomyoma or prolapsing submucosal fibroid
- Urinary symptoms or signs such as hydronephrosis after complete evaluation
- Infertility with leiomyomas as the only abnormal finding
- Recurrent pregnancy loss with distortion of the endometrial cavity
- Markedly enlarged uterine size with compression symptoms or discomfort

Rapid enlargement of the uterus during the premenopausal years or any increase in uterine size in a postmenopausal woman have been suggested as indications for surgery because

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of the inability to exclude uterine sarcoma. Although the absolute risk of uterine sarcomas developing in a fibroid uterus has been reported to be less than 2 to 3 per 1,000, **one study found sarcomas to be no more common in women with rapid uterine growth than those without such growth** (244). However, rapid enlargement has not been well defined, and serial measurements may be hampered by variations in the interpretation of size by the examiner or series of examiners. A high level of suspicion of pelvic malignancy has been listed as among the indications for surgery, as has growth of leiomyoma after menopause (195).

Hysterectomy has long been viewed as the definitive management of symptomatic uterine leiomyomas (see Chapter 22). Myomectomy is an alternative to hysterectomy for patients who desire childbearing, who are young, or who prefer that the uterus be retained. **Recent studies suggest that the morbidity of abdominal myomectomy and hysterectomy are similar**, although previous reports had suggested higher risks for myomectomy, including the risks of hemorrhage and transfusion requirements (245,246). Blood

loss and risk of transfusion are greater for women with larger uteri (247).

Laparoscopic myomectomy minimizes the size of the abdominal incision, although several small incisions are required. The biggest concerns with laparoscopic myomectomy include the removal of large myomas through small incisions and the repair of the uterus (171).

Instruments that efficiently morcellate the myomas have been developed, although skilled surgical techniques are required. There is controversy as to whether laparoscopic suturing provides strength and healing equivalent to that achieved with laparotomy. Risks include the need to convert to a laparotomy and the risk of uterine rupture with subsequent pregnancy (171).

Vaginal myomectomy is indicated in the case of a prolapsed pedunculated submucous fibroid. Hysteroscopic resection of small submucous leiomyomas is a technique that may offer benefits for a selected group of patients (see Chapter 21). **The risk of recurrence for leiomyomas has been reported to be as high as 50% after myomectomy, with up to one third requiring repeat surgery** (196,248). Endometrial ablation can decrease bleeding for women with primary intramural fibroids and can be performed using a variety of techniques, including laser ablation, thermal ablation, resection, or chemical destruction (171).

The preoperative use of GnRH agonists for both hysterectomy and myomectomy results in a decrease in uterine size. The expense, side effects, and time required to achieve a significant decrease in size are limitations to their use. The use of GnRH agonists may make surgical plans less distinct and thus myomectomy technically more difficult.

Nonextirpative approaches to the management of leiomyomas include myolysis, MRI-directed focused ultrasonography, and uterine artery embolization, although long-term safety and efficacy of these methods have not yet been demonstrated. Myolysis or ablation can be performed with the use of lasers, radiofrequency, needle electrodes, cryoprobes, focused ultrasonography directed by MRI, ultrasonography, or laparoscopy (249).

Uterine artery embolization has been reported to provide short-term relief of bulk-related and bleeding symptoms of leiomyoma, although serious consequences, including infection, massive bleeding, and necrosis requiring emergency surgery have been reported (172,250). Pain is frequently a consequence, and patients should be well informed about possible complications (251). The procedure has been characterized as investigational (171).

Ovarian Masses

The now-routine application of ultrasound technology to gynecologic examinations has led to the more frequent detection of ovarian cysts. Ultrasonography is a relatively easy diagnostic study to perform, but this ease has led to the labeling of physiologic ovarian

morphology, cystic follicles, as pathologic and the subsequent referral of patients for therapies, including surgery, without indications. **Treatment of ovarian masses that are suspected to be functional tumors is expectant. A number of randomized prospective studies have shown no acceleration of the resolution of functional ovarian cysts** (which were associated with the use of clomiphene citrate or human menopausal gonadotropins) **with oral contraceptives compared with observation alone** (212,252,253). **However, oral contraceptives are effective in reducing the risk of subsequent ovarian cysts and may be appropriate for women who desire both contraception and their noncontraceptive benefits.**

Symptomatic cysts should be evaluated promptly, although mildly symptomatic masses suspected to be functional should be managed with analgesics rather than surgery to avoid the development of adhesions that may impair subsequent fertility. Surgical intervention is warranted in the presence of severe pain or the suspicion of malignancy or torsion. **On ultrasonography, large cysts and those that have multiloculations, septa, papillae, and increased blood flow should be suspected of neoplasia. If a malignant mass is suspected at any age, exploratory laparotomy should be performed promptly.**

Ovarian or adnexal torsion is suspected on the basis of peritoneal signs and the acuity of onset. Doppler flow studies suggesting abnormal flow are highly predictive of torsion (254). The absence of internal ovarian flow is not specific to torsion and may be seen with cystic lesions, although in these situations peripheral flow usually can be visualized (255). Visualization of a twisted vascular pedicle has also been shown to be highly predictive (256). Normal flow does not exclude torsion, and in one study 60% of surgically confirmed cases of torsion had normal Doppler flow (257).

The management of suspected ovarian torsion, which can occur at any age from prepubertal to postmenopausal, is surgical. When torsion is confirmed by laparoscopy, untwisting of the mass and ovarian preservation rather than extirpation are generally indicated (258,259) This management is particularly important in prepubertal and young women (260). The value of oophoropexy in preventing recurrent torsion is not well established.

Ultrasonographic or CT-directed aspiration procedures of ovarian masses should not be used in women in whom there is a suspicion of malignancy. In the past, laparoscopic surgery for ovarian masses has been reserved for diagnostic or therapeutic purposes in patients at very low risk for malignancy. Although it is feasible to perform laparoscopic surgical staging and treatment of ovarian low-malignant-potential tumors and early-stage ovarian cancer safely, the role of laparoscopy versus laparotomy in a woman with ovarian cancer

has been debated (261). Concerns related to laparoscopy in managing gynecologic malignancy include the accuracy of intraoperative diagnosis, inadequate resection, significance of tumor spillage, inaccurate or delayed surgical staging, delay in therapy, and the possibility of port-site metastasis. In laparoscopic oophorectomy for presumed benign disease, there is a possibility of a missed diagnosis of malignancy, which would necessitate reexploration, even with frozen section. Whether laparoscopic management results in long-term compromise of outcome is unclear; thus, the laparoscopic management of complex masses that may be malignant remains controversial (262,263,264).

The management of presumed benign ovarian masses with operative laparoscopy is now common (Fig. 14.29), although complication rates are higher with complicated operative laparoscopy procedures such as those required for extensive endometriosis (265,266). **The choice of surgical approach (laparotomy or laparoscopy) should be based on the surgical indications, the patient's condition, the surgeon's expertise and training, informed patient preference, and the most recent data supporting the chosen approach.** The clear advantage of this technique is the shorter hospital stay, shorter recovery time, and lessened postoperative pain (265). Surgical complications include bowel injury, ureteral or other urinary tract injury, cannula site vessel injury, or incisional hernia (267). In one series the overall complication rate was 13.3% (267). Randomized clinical trials evaluating laparoscopy versus laparotomy in the treatment of ovarian masses have been performed and typically demonstrate a shorter hospitalization time with less postoperative pain and a shorter recovery period (224,268,269).

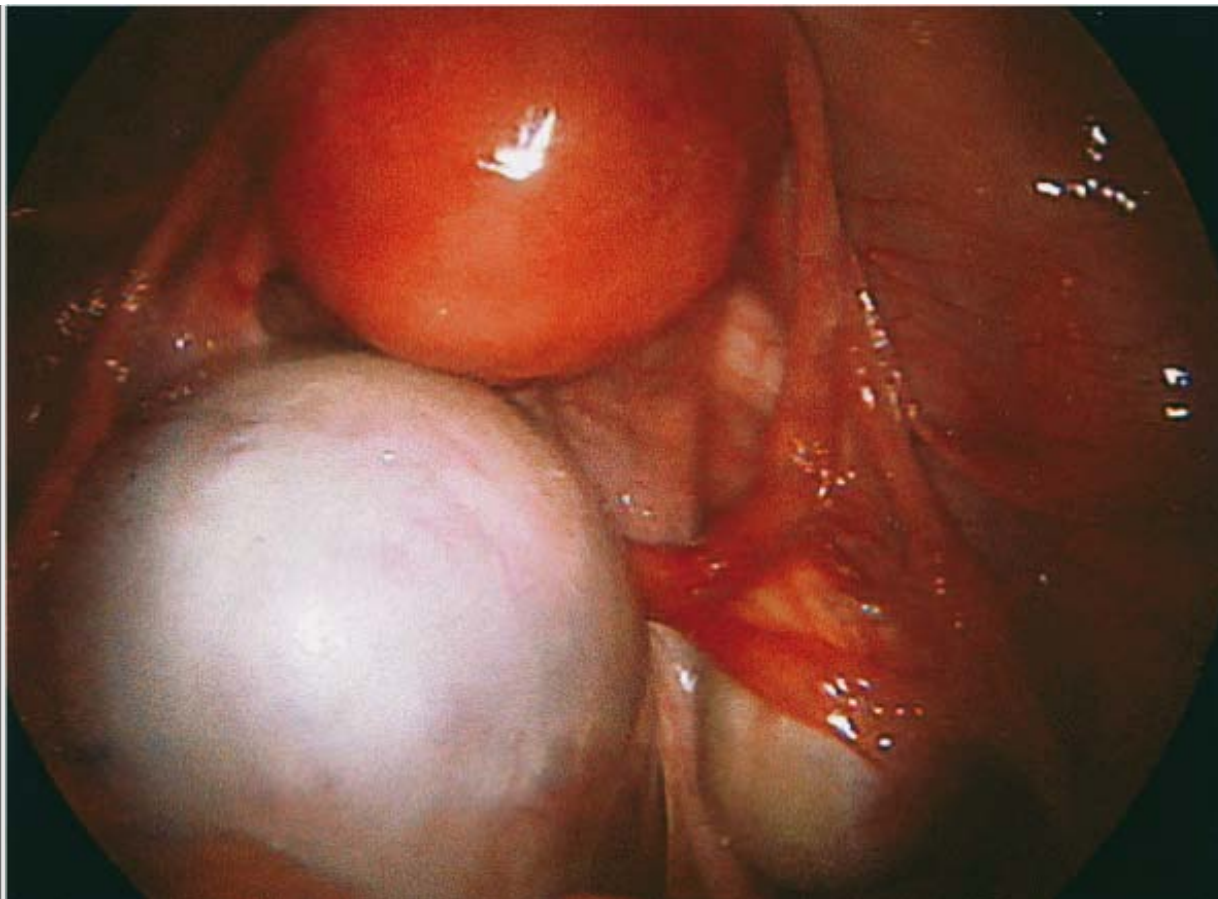


Figure 14.29 Laparoscopic appearance of benign ovarian mass (dermoid cyst).

The role of laparoscopy has been even more controversial in the removal of dermoid cysts than with other benign masses. Concern focuses on prevention of spill of the cyst contents. Randomized clinical trials have been reported with variable findings regarding spill; some studies suggest that cyst contents are more likely to spill with laparoscopy, whereas others do not find a difference or note no increase in morbidity when spillage occurred (270,271,272). Culdotomy and the use of an endoscopic specimen bag have been associated with lower rates of tumor spillage (272,273).

Vulvar Conditions

In postmenarchal individuals, vulvar symptoms are most often related to a primary vaginitis and a secondary vulvitis. The mere presence of vaginal discharge can lead to vulvar irritative symptoms, or candidal vulvitis may be present (Fig. 14.30). The causes of vaginitis and cervicitis

are covered in Chapter 16. Adult women describe vulvar symptoms using a variety of terms (itching, pain, discharge, discomfort, burning, external dysuria, soreness, pain with intercourse or sexual activity). **Burning with urination from noninfectious causes may be difficult to distinguish from a urinary tract infection, although some women can distinguish pain when the urine hits the vulvar area (an external dysuria) from burning pain (often suprapubic in location) during urination.** Itching is a very common vulvar symptom. A variety of vulvar conditions and lesions can present with pruritus. As in adolescents, vulvovaginal symptoms may be caused by STDs, nonsexually transmitted vaginitis, or UTI. The distinction between symptoms related to a UTI and those of vaginitis is difficult, and consideration should be given to testing for both *C. trachomatis* and obtaining a urine culture, particularly in young reproductive-age women (125).





Figure 14.30 Candidal vulvitis.

A number of skin conditions that occur on other areas of the body may occur on the vulvar area. Table 14.9 contains a list of these conditions classified by either infectious or noninfectious causes. Whereas the diagnosis of some of these conditions is apparent from inspection alone (e.g., a skin tag) (Fig. 14.31), any lesions that appear atypical or in which the diagnosis is not clear should be analyzed by biopsy, as the risks of malignant lesions increases with age.

Pigmented vulvar lesions include benign nevi (Fig. 14.32), lentiginos, melanosis, seborrheic keratosis, condyloma, and some vulvar intraepithelial neoplasias (VIN), especially multifocal VIN 3. **Suspicious pigmented vulvar lesions in particular should warrant biopsy to rule out VIN or malignant melanoma** (274). Approximately 10% of white women have a pigmented vulvar lesion; some of these lesions may be malignant (see Chapter 36) or have the potential for progression (VIN) (see Chapter 17). There has been an increase in rates of VIN in women younger than age 50, along with increasing rates of vulvar squamous cell carcinoma *in situ*, possibly related to increasing rates of human papillomavirus infection. Heightened awareness among clinicians may play a role in the increasing frequency of diagnosis; suspicious lesions warrant vulvar biopsy.

The behavior of some nevocellular lesions (representing about 2% of nevi) is not well established but has been linked to melanoma (275). Multiple hyperpigmented lesions of typical lentigo simplex and melanosis are common, and any areas with irregular borders should be evaluated by biopsy.

Table 14.9 Subacute and Chronic Skin Recurrent Conditions of the Vulva

<i>Noninfectious</i>	<i>Infectious</i>
Acanthosis nigricans	Cellulitis
Atopic dermatitis	Folliculitis
Behçet's disease	Furuncle/carbuncle
Contact dermatitis	Insect bites (e.g., chiggers, fleas)
Crohn's disease	Necrotizing fasciitis
Diabetic vulvitis ^a	Pubic lice
Hidradenitis suppurativa ^a	Scabies
Squamous cell hypertrophy	Tinea
Lichen sclerosus	
Paget's disease	
"Razor bumps"—folliculitis or pseudofolliculitis	
Psoriasis	
Seborrheic dermatitis	
Vulvar aphthous ulcer	
Vulvar intraepithelial neoplasia	
^a Etiology unknown, often secondarily infected.	

Vulvar Biopsy

A vulvar biopsy is essential in distinguishing benign from premalignant or malignant vulvar lesions, especially because many types of lesions may have a somewhat similar appearance. Vulvar biopsies should be performed liberally in women of reproductive age to ensure that these lesions are diagnosed and treated appropriately. A prospective study of vulvar lesions evaluated by biopsy in a gynecologic clinic found lesions occurring in the following order of frequency: epidermal inclusion cyst, lentigo, Bartholin duct obstruction, carcinoma *in situ*, melanocytic nevi, acrochordon, mucous cyst, hemangiomas, postinflammatory hyperpigmentation, seborrheic keratoses, varicosities, hidradenomas, verruca, basal cell carcinoma, and unusual tumors such as neurofibromas, ectopic tissue, syringomas, and abscesses (276). Clearly, the frequency with which a lesion would be reported after a tissue biopsy is related to the frequency with which all lesions of a given pathology are evaluated in this manner. Thus, this listing probably underrepresents such common lesions as condylomata (see Fig. 14.16).



Figure 14.31 Large benign skin tag from left labium majus.



Figure 14.32 Pigmented vulvar lesion.

Biopsy is easily performed in the office using a local anesthetic. Typically, 1% lidocaine is infiltrated beneath the lesion using a small (25- to 27-gauge) needle. Disposable punch biopsy instruments come in a variety of sizes from 2 to 6 mm in diameter. They have the advantage of being sharp and thus facilitate obtaining a good specimen. Sterilizable instruments also are available and may be a more ecologically sound choice if they can be maintained and sharpened periodically. These skin biopsy instruments, along with fine forceps, scissors, and a scalpel, should be available in all outpatient gynecologic settings. For smaller biopsies, it is usually not necessary to place a suture. Topical silver nitrate can be used for hemostasis. Multiple tissue samples may be appropriate to obtain representative areas of a lesion if the lesion has a variable appearance or is multifocal. Although the vulvar biopsy procedure involves minimal discomfort, the biopsy sites will be painful for several days after the procedure. The prescription of a topical anesthetic such as 2% lidocaine jelly, to be applied periodically and before urinating, is appreciated by patients who require this

procedure. Infection of the site can occur, and patients should be cautioned to report excessive erythema or purulent drainage.

Other Vulvar Conditions

Classification and description of intraepithelial lesions of the vulva are presented in Chapter 17.

Pseudofolliculitis

This is similar to what has been described as pseudofolliculitis barbae (razor bumps), may occur in women who follow the increasingly popular practice of

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shaving pubic hair (276). **Pseudofolliculitis consists of an inflammatory reaction surrounding an ingrown hair and occurs most commonly among individuals with curly hair, particularly African Americans.**

Fox-Fordyce Disease

This condition is characterized by a chronic, pruritic eruption of small papules or cysts formed by keratin-plugged apocrine glands. It is commonly present over the lower abdomen, mons pubis, labia majora, and inner portions of the thighs. **Hidradenitis suppurativa is a chronic condition involving the apocrine glands with the formation of multiple deep nodules, scars, pits, and sinuses that occur in the axilla, vulva, and perineum.** Hyperpigmentation and secondary infection are often seen. Hidradenitis suppurativa can be extremely painful and debilitating. It is often treated with antibiotics (with coverage of both aerobic and anaerobic bacteria). Estrogens or antiandrogen therapy has been attempted; surgical therapy with wide local excision may be necessary. Therapy with isotretinoin and steroids has been reported to be successful (277,278).

Acanthosis nigricans

This disease involves widespread velvety pigmentation in skin folds, particularly the axillae, neck, thighs, submammary area, and vulva and surrounding skin (Fig. 14.33). It is of particular interest to gynecologists because of its association with hyperandrogenism and PCOS; as such, it is associated with obesity, chronic anovulation, acne, glucose intolerance, and cardiovascular disease (150,279). Several drugs, including *metformin*, *octreotide*, *retinoids*, and *topical cholecalciferol* (vitamin D₃) analogs, are also beneficial in treating acanthosis

nigricans (280).

Extramammary Paget's Disease

This is an intraepithelial neoplasia containing vacuolated Paget's cells (see Chapter 17). Clinically, it may have an appearance varying from moist, oozing ulcerations to an eczematoid lesion with scaling and crusting, to a grayish lesion (39). A biopsy to confirm the diagnosis is mandatory.



Figure 14.33 Acanthosis nigricans.

Vulvar Intraepithelial Neoplasia

VIN is associated with human papillomavirus infection and is increasing in frequency, particularly among young women (see Chapter 17) (281). Diagnosis requires biopsy of any suspicious vulvar lesions, particularly those that are pigmented or discolored. The increasing frequency of this entity dictates a careful vulvar inspection during annual gynecologic examinations.

Vulvar Tumors, Cysts, and Masses

Condylomata acuminata

These are very common vulvar lesions and are usually easily recognized and treated with topical therapies such as *trichloroacetic* and *bichloroacetic acid*. Other sexually transmitted organisms, such as the virus responsible for molluscum contagiosum and the lesions of syphilis and condylomata lata, may occasionally be mistaken for vulvar condylomata acuminata caused by human papillomavirus (see Chapter 16). A summary of benign vulvar tumors is listed in Table 14.10. There is argument regarding whether sebaceous cysts exist on the vulva or whether these lesions are histopathologically epidermal or epidermal inclusion cysts (282). So-called sebaceous cysts are clinically indistinguishable from epidermal inclusion cysts that may result from the burial of fragments of skin after the trauma of childbirth or episiotomy, or that arise from occluded pilosebaceous ducts. These cysts are seldom symptomatic, although if infection develops, incision and drainage may be required.

It has been argued that the commonly cited concept of milk lines extending into the vulva and accounting for lesions of mammarylike anogenital glands (e.g., fibroadenoma, lactating glands) is not supported by observations in human embryos; such studies show that primordia of the mammary glands do not extend beyond the axillary-pectoral area (283). Eccrine or apocrine glands have been suggested as the probable source of these unusual lesions.

Table 14.10 Types of Vulvar Tumors

1. Cystic lesions	3. Anatomic
Bartholin duct cyst	Hernia
Cyst in the canal of Nuck (hydrocele)	Urethral diverticulum
Epithelial inclusion cyst	Varicosities
Skene duct cyst	4. Infections
2. Solid tumors	Abscess—Bartholin, Skene, periclitral, other
Acrochordon (skin tag)	Condyloma lata
Angiokeratoma	Molluscum contagiosum
Bartholin gland adenoma	Pyogenic granuloma
Cherry angioma	5. Ectopic
Fibroma	Endometriosis
Hemangioma	Ectopic breast tissue
Hidradenoma	
Lipoma	
Granular cell myoblastoma	
Neurofibroma	
Papillomatosis	

Bartholin Duct Cysts

These are common vulvar lesions. They result from occlusion of the duct with accumulation of mucus and are frequently asymptomatic. Infection of the gland may result in the accumulation of purulent material, with the formation of a rapidly enlarging, painful, inflammatory mass (a Bartholin abscess). An inflatable bulb-tipped catheter has been described by Word and is quite easy to use (284). The small catheter is inserted through a small stab wound into the abscess after infiltration of the skin with local anesthesia; the balloon of the catheter is inflated with 2 to 3 mL of saline and the catheter remains in place for 4 to 6 weeks, allowing epithelialization of a tract and the creation of a permanent gland opening.

Skene's Duct Cysts

These are cystic dilations of the Skene glands, typically located adjacent to the urethral meatus within the vulvar vestibule. Although most are small and often asymptomatic, they may enlarge and cause urinary obstruction, requiring excision.

Painful Intercourse

Painful intercourse (dyspareunia) may be caused by many different vulvovaginal conditions, including common vaginal infections and vaginismus (see Chapters 11 and 15). A careful sexual history is essential, as is a careful examination of the vulvar area and vagina. *Vulvodynia* is the term used to describe unexplained vulvar pain, sexual dysfunction, and the resultant psychological disability (285). **The term *vulvar vestibulitis* has been used to describe a situation in which there is pain during intercourse, primarily during entry** (286,287,288). The condition is characterized by tender areas surrounding the vulvar vestibule and hymenal ring (see Chapter 15). A number of recent studies have failed to demonstrate a consistent relationship with any genital infectious organism, including *C. trachomatis*, gonorrhea, *Trichomonas*, mycoplasma, *Ureaplasma*, *Gardnerella*, candida, or human papillomavirus (289,290,291). Although the symptoms of dyspareunia with insertion can be disabling, no curative therapies have been found. Both medical and behavioral therapies are of some benefit, and although some authors encourage surgery, this treatment is controversial (292,293). The visible lesion of vestibular papillomatosis may be a nonspecific response to discharge or inflammation.

Vulvar Ulcers

A number of STDs can cause vulvar ulcers, including herpes simplex virus, syphilis, lymphogranuloma venereum, and granuloma inguinale (see Chapter 16). *Crohn's disease* can include vulvar involvement with abscesses, fistulae, sinus tracts, fenestrations, and other scarring. Although medical treatment with systemic steroids and other systemic agents is the mainstay of therapy, surgical therapy of both intestinal and vulvar disease may be required.

Behçet's Disease

This condition is characterized by genital and oral ulcerations with ocular inflammation (294). The cause and the most effective therapy are not well established (295).

Lichen Planus

This condition causes oral and genital ulcerations. Typically, there is desquamative vaginitis with erosion of the vestibule. Treatment is based on the use of both topical and systemic steroids. Plasma cell mucositis appears as erosions in the vulvar area, particularly the vestibule. Biopsy is essential in establishing the diagnosis.

Vaginal Conditions

Vaginal discharge is one of the most common vaginal symptoms. Conditions ranging from vaginal candidiasis to chlamydia cervicitis to bacterial vaginosis to cervical carcinoma may cause vaginal discharge. Infectious vaginal conditions are addressed more completely in Chapter 16. Vaginal lesions may occasionally be palpable to a woman. More commonly, vaginal lesions are discovered on examination by a clinician. They may contribute to symptoms (such as bleeding or discharge), or they may be entirely asymptomatic.

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Vaginitis, cervicitis, and vaginal or cervical lesions (including malignancies) can be causes of vaginal discharge. Other noninfectious causes of discharge are as follows:

- **Retained foreign body—tampon, pessary**
- **Ulcerations—tampon-induced, lichen planus, herpes simplex infection**
- **Malignancy—cervical, vaginal**

Some vaginal lesions are asymptomatic and are noted incidentally on examination. Fibroepithelial polyps consist of polypoid folds of connective tissue, capillaries, and stroma covered by vaginal epithelium. Although they can be excised easily in the office, their vascularity can be troublesome, and excision is not necessary unless the diagnosis is in question. **Cysts of embryonic origin can arise from mesonephric, paramesonephric, and urogenital sinus epithelium. Gartner's duct cysts are of mesonephric origin and are usually present on the lateral vaginal wall.** They rarely cause symptoms and, therefore, do not require treatment. Other embryonic cysts can arise anterior to the vagina and beneath the bladder. Cysts that arise from the urogenital sinus epithelium are located in the area of the vulvar vestibule. Vaginal adenosis, the presence of epithelial-lined glands within the vagina, has been associated with *in utero* exposure to diethylstilbestrol. No therapy is necessary, other than close observation and periodic palpation to detect nodules that may need to be evaluated by biopsy to rule out vaginal clear cell adenocarcinoma (see Chapter 34).

Women will sometimes describe a bulging lesion of the vagina and vulvar area, variably associated with symptoms of pressure or discomfort. The most common cause of such a lesion

is one of the disorders of vaginal support: cystocele, rectocele, or urethrocele. Management of these conditions is discussed in Chapter 24. Other genital lesions, such as urethral diverticula or occasionally embryonic cysts, may cause similar symptoms.

Postmenopausal Age Group

Abnormal Bleeding

Differential Diagnosis

The causes of postmenopausal bleeding and the percentage of patients who seek treatment for different conditions are presented in Table 14.11.

<i>Factor</i>	<i>Approximate Percentage</i>
Exogenous estrogens	30
Atrophic endometritis/vaginitis	30
Endometrial cancer	15
Endometrial or cervical polyps	10
Endometrial hyperplasia	5
Miscellaneous (e.g., cervical cancer, uterine sarcoma, urethral caruncle, trauma)	10

From **Hacker NF, Moore JG**. *Essentials of obstetrics and gynecology*. 3rd ed. Philadelphia, PA: WB Saunders, 1998:635, with permission.

Benign Disorders

Women who are taking hormone therapy during menopause may be using a variety of hormonal regimens that can result in bleeding (see Chapter 32). Because unopposed estrogen therapy can result in endometrial hyperplasia, various regimens of progestins are typically added to the estrogen regimen; they may be given in a continuous or periodic fashion (296). It has been suggested that endometrial sampling is indicated for any

unexpected bleeding that occurs with hormonal therapy. **A significant change in withdrawal bleeding or breakthrough bleeding (e.g., absence of withdrawal bleeding for several months followed by resumption of bleeding or a marked increase in the amount of bleeding) should prompt endometrial sampling.**

Patient compliance has been a significant issue with hormone therapy. Missed doses of medication and failure to take the medication in the prescribed fashion can lead to irregular bleeding or spotting that is benign in origin but that can result in patient dissatisfaction (297).

The problems that women most often report with hormone therapy include vaginal bleeding and weight gain. The use of a continuous low-dose combined regimen has the advantage that for many women, bleeding will ultimately cease after several months, during which irregular and unpredictable bleeding may occur (298). Some women are unable to tolerate these initial months of irregular bleeding. The risk of endometrial hyperplasia or neoplasia with this regimen appears to be low.

Other benign causes of bleeding include atrophic vaginitis as well as endometrial and cervical polyps, which may become apparent as postcoital bleeding or spotting. Women who experience bleeding after menopause may attempt to minimize the extent of the problem; they may describe only "spotting" or "pink or brownish discharge." However, any indication of bleeding or spotting should be evaluated. **In the absence of hormone therapy, any bleeding after menopause (classically defined as absence of menses for 1 year) should prompt evaluation with endometrial sampling.** At least one fourth of postmenopausal women with bleeding have a neoplastic lesion. Endometrial polyps and other abnormalities can be seen in women who are taking tamoxifen. These polyps are more likely to involve cystic dilation of glands, stromal condensation around the glands, and squamous metaplasia of the overlying epithelium (299). These polyps can be benign, although they must be distinguished from endometrial malignancies, which may also occur with this medication. The incidence of endometrial polyps not associated with tamoxifen increases with age during the reproductive years; it is not clear, however, whether the incidence subsequently peaks or decreases during the postmenopausal years (151). Endometrial polyps are more likely to be malignant in postmenopausal women, and hypertension has been associated with an increased risk of malignancy (159).

Neoplasia

Endometrial, cervical, and ovarian malignancies must be ruled out in the presence of postmenopausal bleeding. **A Pap test is essential when postmenopausal bleeding is noted, although the Pap test is an insensitive diagnostic test for detecting endometrial cancer.** The Pap test results are negative in some cases of invasive cervical

carcinoma because of tumor necrosis.

Cervical malignancy is diagnosed by cervical biopsy of grossly visible lesions and colposcopically directed biopsy for women with abnormal Pap test results (see Chapter 17). **Functional ovarian tumors may produce estrogen and lead to endometrial hyperplasia or carcinoma, which may cause bleeding.**

Diagnosis

Pelvic examination to detect local lesions and a Pap test to assess cytology are essential first steps in finding the cause of postmenopausal bleeding. Pelvic ultrasonographic examination

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and, in particular, vaginal ultrasonography or sonohysterography can suggest the cause of bleeding (300,301). **Endometrial sampling, through office biopsy, hysteroscopy, or D & C, is usually considered essential. Initial biopsy done in the office is more cost-effective than D & C, surgery, or observation alone** (302). The cost-effectiveness of other screening strategies, including transvaginal ultrasonography or sonohysterography, has not been well studied. It has been suggested that an endometrial thickness of less than 6-10 mm measured by transvaginal ultrasonography is unlikely to indicate endometrial cancer. A meta-analysis of studies comparing endometrial pathology with ultrasonography findings suggested that an endometrial thickness of less than 6 mm essentially excludes malignancy (303).

Management

Benign Disorders

The management of bleeding caused by atrophic vaginitis includes topical or systemic use of estrogens after other causes of abnormal bleeding have been excluded. Cervical polyps can easily be removed in the office.

Endometrial Hyperplasia

The terminology used to describe endometrial hyperplasia is confusing, and the clinician must consult with the pathologist to ensure an understanding of the diagnosis. **The following lesions are considered to be benign: *anovulatory, proliferative, cystic glandular hyperplasia, simple cystic hyperplasia, simple hyperplasia, and adenomatous hyperplasia without atypia.*** These terms reflect and describe

an exaggerated proliferative response of the endometrium. In most cases, benign endometrial hyperplasia is resolved with D & C or progestin therapy.

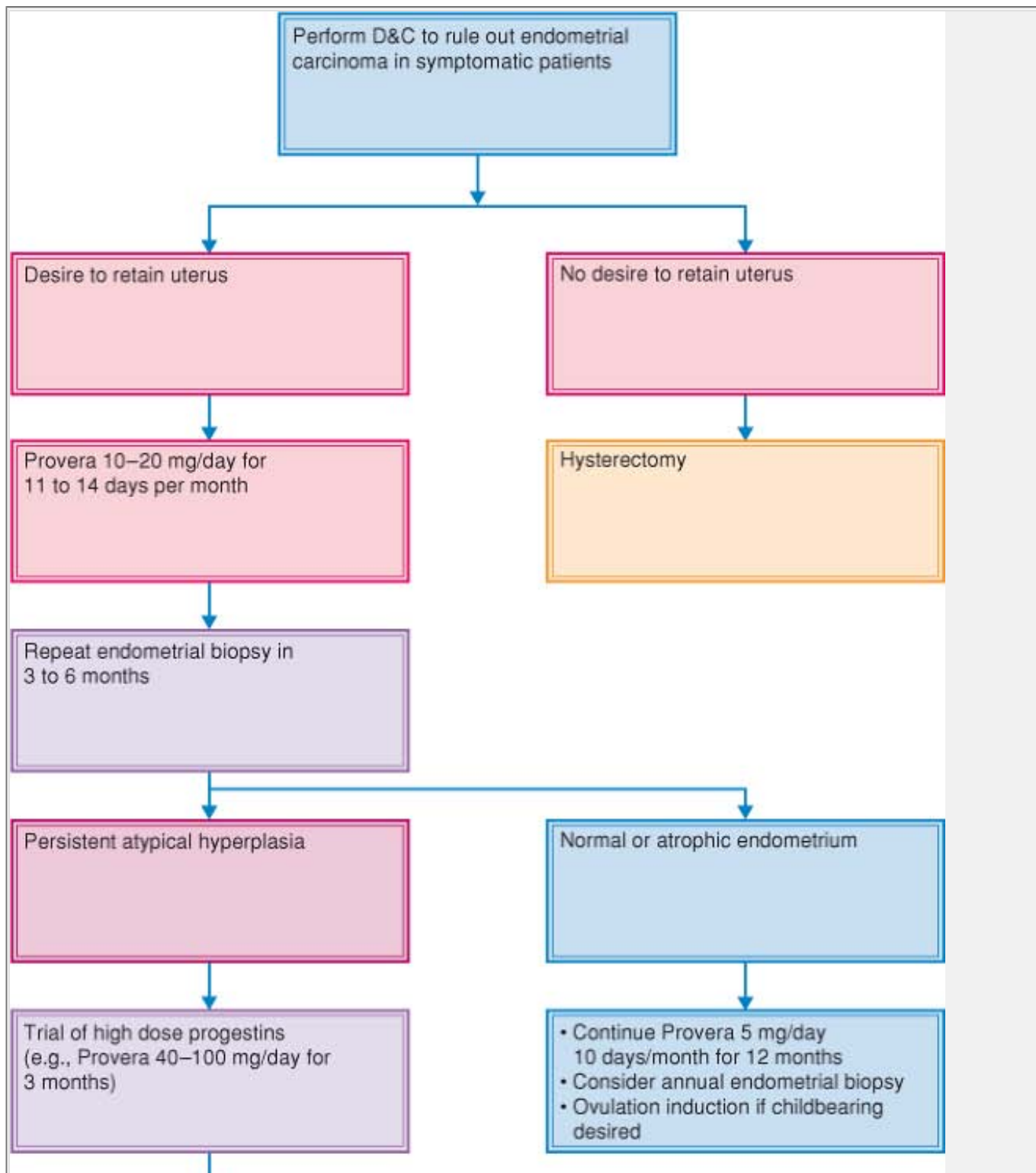
Repeat surveillance with endometrial biopsy may be warranted.

The presence of atypia with abnormal proliferation, including features of back-to-back crowding of the glands with epithelial activity demonstrated by papillary projections into the glands, is associated with an increased risk of progression to endometrial carcinoma. These architectural abnormalities may be associated with individual cellular atypia (enlarged, irregular nuclei, chromatin clumping, and prominent nucleoli). The presence of mitotic activity also can be variable.

The management of endometrial hyperplasia is based on an understanding of the natural history of the lesion involved. In one study, only 2% of 122 patients with hyperplasia without cytologic atypia progressed to carcinoma, whereas 23% of those with atypical hyperplasia subsequently developed carcinoma (304).

Architectural complexity and crowding appears to place patients at greater risk for progression than does the presence of cytologic atypia alone. Atypical endometrial hyperplasia is considered part of a continuum with endometrial cancer, and there is a concern that the diagnosis remains uncertain as long as the uterus is *in situ* (183). Hysterectomy is recommended for treatment of atypical endometrial hyperplasia in postmenopausal women.

Data suggest that most women with endometrial hyperplasia without atypia will respond to progestin therapy and are not at increased risk of developing cancer (305). Patients who do not respond are at a significantly increased risk of progressing to invasive cancer and should be advised to have a hysterectomy. Patients who are less likely to respond can be identified on the basis of cytologic atypia. Progestin therapy may be used in women with atypical endometrial hyperplasia who are poor operative candidates, and these women should initially have an endometrial biopsy every 3 months to check for recurrence (183). A suggested scheme of management is outlined in Figure 14.34. This treatment is discussed in more detail in Chapter 33.



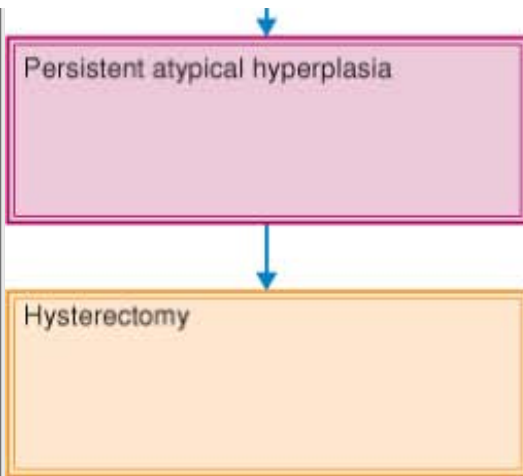


Figure 14.34 Management of endometrial hyperplasia. (From **Berek JS, Hacker NF.** *Practical gynecologic oncology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005:422, with permission.)

Pelvic Mass

Differential Diagnosis

Ovarian Masses

During the postmenopausal years, the ovaries become smaller (219):

- *Before menopause, the dimensions are approximately 3.5 × 2 × 1.5 cm.*
- *In early menopause, the ovaries are approximately 2 × 1.5 × 0.5 cm.*
- *In late menopause, they are even smaller: 1.5 × 0.75 × 0.5 cm.*

The postmenopausal palpable ovary (PMPO) syndrome is based on the concept that any ovary that

is palpable on examination beyond menopause is abnormal and deserves evaluation (306); however, this finding has not been shown to be a reliable predictor of malignancy (see Chapter 35). Clearly, body habitus makes a difference in the ease of examination, but a postmenopausal ovary that, on palpation, is comparable in size to a premenopausal ovary is abnormally large. Ovarian cancer is predominantly a disease of postmenopausal women; the incidence increases with age, and the average patient age is about 56 to 60 years (see Chapter 35).

With increased use of pelvic ultrasonographic evaluation, a new problem has arisen in postmenopausal women: the discovery of a small ovarian cyst. This is particularly troublesome in a woman who is entirely asymptomatic and whose ultrasonographic examination was performed for indications unrelated to pelvic pathology. It has been suggested that **when the cyst is asymptomatic, small (less than 5 cm in diameter), unilocular, and thin walled, with a normal CA125 level, the risk of malignancy is extremely low and these masses can be followed conservatively, without surgery** (307,308). Surgery may be indicated in some women with a strong family history of ovarian, breast, endometrial, or colon cancer, or a mass that appears to be enlarging (see Chapter 35). The addition of color flow Doppler examination and other ultrasonographic characteristics may be helpful in distinguishing benign from malignant masses (309,310) (Table 14.8).

Uterine and Other Masses

In women who have been receiving regular gynecologic care, the discovery of a new pelvic mass after menopause is worrisome because the likelihood of malignant neoplasm is high if it is an ovarian tumor. Many postmenopausal women have not had regular gynecologic care, however, so the discovery of a mass may reflect the persistence of uterine leiomyoma that had not previously been discovered. Some women may not remember having been told they had a pelvic mass. Thus, **a review of medical records may be helpful in determining the preexistence of a benign pelvic mass.** Uterine leiomyomas are hormonally responsive and typically decrease in size or resolve after menopause. An increased risk of leiomyomas has been demonstrated with the menopausal use of hormone therapy, and leiomyomas may be less likely to decrease in size or even to increase in size with hormone therapy (151). Other benign masses can occur in this age group, including paraovarian cysts and unusual tumors, such as benign retroperitoneal cysts of müllerian type (311). The risk of leiomyosarcomas increases with age, and benign leiomyoma may coexist with leiomyosarcomas.

Diagnosis

A personal and family medical history is helpful in detecting individuals at increased risk for the development of ovarian cancer. Several hereditary family cancer syndromes involve ovarian neoplasms (see Chapter 35). However, **patients with hereditary forms of epithelial ovarian cancer account for only a small percentage of all cases; 90% to 95% of cases of ovarian cancer are sporadic and without identifiable heritable risk.**

In postmenopausal women with a pelvic mass, a CA125 measurement may be helpful in predicting a higher likelihood of a malignancy, which may guide decisions regarding management, consultation, or referral (312). Currently, a high index of suspicion by both women and their clinicians represents that best way to detect early ovarian cancer. Persistent symptoms such as an increase in abdominal size, bloating, fatigue, abdominal pain, indigestion, inability to eat normally, urinary frequency, pelvic pain, constipation, back pain, new onset of urinary incontinence, or unexplained weight loss require evaluation and consideration of the possibility of ovarian cancer. A physical examination, transvaginal ultrasonography, and CA125 measurement are appropriate. **A normal CA125 level does not rule out ovarian cancer; up to 50% of early-stage ovarian malignancies and 20% to 25% of advanced cancers have normal values of CA125** (312).

Management

The use of improved imaging techniques may allow the nonoperative management of ovarian masses that are probably benign (Table 14.8). **A suspicious or persistent complex mass requires surgical evaluation. A physician trained to appropriately stage and debulk ovarian cancer, such as a gynecologic oncologist, should perform the surgery in a hospital with the necessary support and consultative services to optimize the patient's outcome** (312). **When a malignant ovarian mass is discovered and the appropriate operation cannot be performed by the generalist obstetrician–gynecologist, a gynecologic oncologist should be consulted. Comprehensive surgical staging facilitates appropriate therapy and optimizes prognosis.**

Vulvar Conditions

Anatomic changes that occur in postmenopausal women include atrophy of the labia majora and increasing prominence of the labia minora. The epithelium of the hymen and vestibule become thin; there is a shift in vaginal cellular maturation in response to estrogen deprivation, with resultant thinning. Although these changes lead to minimal symptoms in most women, external dysuria, pruritus, tenderness, dyspareunia, and bleeding can result from fissuring

and excoriations. **Because of the risk of VIN and malignancy, suspicious lesions require vulvar biopsy.**

Vulvar Dystrophies

Several vulvar conditions occur most commonly in postmenopausal women. Symptoms are primarily itching and vulvar soreness, in addition to dyspareunia.

In the past, numerous terms have been used to describe disorders of vulvar epithelial growth that produce a number of nonspecific gross changes. These terms have included *leukoplakia*, *lichen sclerosus et atrophicus*, *atrophic* and *hyperplastic vulvitis*, and *kraurosis vulvae*.

The malignant potential of the vulvar dystrophies is less than 5%; at particular risk is the patient with cellular atypia on initial biopsy. The International Society for the Study of Vulvar Diseases (ISSVD) has recommended a classification of vulvar dystrophies (see Chapter 17).

Squamous Hyperplasia

Squamous hyperplasia is seen most often in postmenopausal women but may occur during the reproductive years. Pruritus is the most common symptom. The lesion appears thickened and hyperkeratotic, and there may be excoriation. Squamous hyperplasia tends to be discrete but may be symmetric and multiple. Biopsy is necessary to confirm the diagnosis and to evaluate the presence of atypia and exclude malignancy. The relationship of nonneoplastic epithelial disorders of the vulva to malignancy is controversial.

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In managing vulvar symptoms, aggravating factors such as vaginal discharge and environmental factors should be evaluated and managed with local comfort measures and hygiene. Corticosteroid lotions, ointments, and creams are the mainstay of treatment for squamous cell hyperplasia. Medium-potency fluorinated steroids are usually effective in alleviated pruritus; this therapy can be switched to a lower potency hydrocortisone to avoid steroid-induced atrophy that can be associated with prolonged use of fluorinated steroids.

Lichen Sclerosus

Lichen sclerosus is the most common white lesion of the vulva. Lichen sclerosus can occur at any age, although it is most common among postmenopausal women and prepubertal girls. The symptoms are pruritus, dyspareunia, and burning. Lichen sclerosus characteristically is associated with decreased subcutaneous fat to the extent that

the vulva is atrophic with small or absent labia minora, obliteration of the anatomic landmarks, thin labia majora, and sometimes phimosis of the prepuce. The surface is pale with a shiny, crinkled pattern, often with fissures and excoriation. The lesion tends to be symmetric and often extends to the perineal and perianal areas. The diagnosis is confirmed by biopsy. Invasive cancer has been associated with lichen sclerosus.

Treatment is with an ultrapotent topical steroid such as 0.05% clobetasol.

Approximately 80% of patients respond satisfactorily (313). Maintenance therapy is important and may include the use of a lower potency steroid or the use of a topical emollient (314).

Urethral Lesions

The urethra and vagina have a common embryonic origin and are steroid-dependent tissues. Urethral caruncles and prolapse of the urethral mucosa are examples of vulvar lesions that may be seen in other age groups, but that occur more commonly among older women. Both conditions can be treated with topical or systemic estrogen preparations. Various vulvar skin lesions, including seborrheic keratoses and cherry hemangiomas (senile hemangiomas), occur more commonly on aging skin.

Vaginal Conditions

Up to 40% of postmenopausal women have symptoms of atrophic vaginitis.

Symptoms include an external dysuria, pruritus, tenderness, dyspareunia, and bleeding from fissuring or ulcerations. In addition to the clinical findings of a shiny, flat, thin-appearing vaginal mucosa without rugae, microscopic examination of vaginal secretions reveals an increased number of white blood cells. **Treatment with local or systemic estrogens effectively manages the symptoms and restores normal pH levels with ongoing therapy.** Systemic absorption does occur with topical estrogen therapy, and rates of absorption differ depending on the degree of atrophy. Topical emollients may be helpful if estrogens are not desired or are contraindicated.

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15

Pelvic Pain and Dysmenorrhea

Andrea J. Rapkin

Candace N. Howe



- Acute pelvic pain is rapid in onset, often associated with unstable vital signs and obvious abnormalities on physical examination and laboratory assessment. Improper diagnosis can result in significant morbidity and even mortality.
- Timely and thorough assessment, guided by organ system (reproductive, gastrointestinal, urinary) and type of pathologic category (infection, obstruction, torsion, rupture, neoplasm, pregnancy related) will insure effective diagnosis and management.
- Chronic pelvic pain is debilitating and can affect all aspects of physical and psychosocial functioning. The complex pathophysiology and symptom presentation is characterized by neurological, psychological, and behavioral alterations. Because of the shared innervation and functional interconnections between the pelvic viscera, somatic structures, and the central nervous system, more than one system is generally involved.
- A caring, supportive, and well-informed multidisciplinary approach is crucial for appropriate diagnosis and successful treatment of chronic pelvic pain.

A thorough history and physical examination are extremely important to successful management of both chronic and acute pain, although the specific foci of each differ, as do the ancillary laboratory and diagnostic procedures performed to diagnose acute, life-threatening processes as opposed to chronic pain conditions.

Pelvic pain is the most challenging symptom confronting the practitioner. The problems of acute, cyclic, and chronic pelvic pain encompass a large proportion of gynecologic symptoms. The etiology of gynecologic sources of pelvic pain are diverse and can be further complicated by the similar, and sometimes concurrent, symptoms of gastrointestinal, urological, musculoskeletal, and psychological origins.

Definitions

Acute pain is intense and characterized by sudden onset, sharp rise, and short course. **Cyclic pain** refers to pain that occurs with a definite association to the menstrual cycle. **Dysmenorrhea**, or painful menstruation, is the most common cyclic pain phenomenon and is classified as **primary** or **secondary** on the basis of associated anatomic pathology (1). **Chronic pelvic pain** has been defined as pain of greater than 6 months in duration, localized to the anatomic pelvis, and severe enough to cause functional disability or necessitating medical care (2,3). Whereas acute pain is often associated with profound autonomic reflex responses, such as nausea, emesis, diaphoresis, and apprehension, obvious autonomic reflex responses are not present in chronic pelvic pain. In addition, acute pelvic pain often is associated with signs of inflammation or infection, such as fever and leukocytosis, which are absent in chronic pain states. The pathophysiology of acute pelvic pain involves mediators of inflammation present in high concentration as a result of infection, ischemia, or chemical irritation (4,5,6). By contrast, the etiology of chronic pelvic pain often is obscure. Additionally, chronic pain is characterized by physiologic, affective, and behavioral responses that are quite different from those associated with acute pain (7,8). Acute pain, if inadequately treated and repetitive, can set up an environment of chronic neurogenic inflammation, which results in hyperalgesia and allodynia via neuroplastic changes and ultimately contributes to chronic pelvic pain (6,9,10,11).

Acute Pain

The differential diagnosis of acute pelvic pain is outlined in Table 15.1. Assessing the character of the pain is helpful in creating a differential diagnosis. **Rapid onset of pain is most consistent with perforation of a hollow viscus or ischemia. Colic or severe cramping pain is commonly associated with muscular contraction or obstruction of a hollow viscus, such as intestine or uterus, whereas pain perceived over the entire abdomen suggests a generalized reaction to an irritating fluid within the peritoneal cavity such as blood, purulent fluid, or contents of an ovarian cyst.**

The viscera are relatively insensitive to pain. The first perception of visceral pain is a vague, deep, poorly localizable sensation associated with autonomic reflex responses; however, once the pain becomes localized, the pain is called *referred pain*. Referred pain is well localized and superficial. It is appreciated within the nerve distribution or dermatome of the spinal cord segment innervating the involved viscus. The location of the referred pain provides insight into the location of the primary disease process. The innervation of the pelvic organs is outlined in Table 15.2 (12).

Evaluation

In the evaluation of acute pelvic pain, early diagnosis is critical because significant delay increases morbidity and mortality. Central to correct diagnosis is an accurate history (Fig. 15.1). The date and character of the last and previous menstrual periods and the presence of abnormal bleeding or discharge should be ascertained. The menstrual, sexual, and contraceptive history and any history of sexually transmitted conditions and previous gynecologic disorders are important. Pain history should be obtained (2,4,13,14), including how and when the pain started, the presence of gastrointestinal symptoms (eg, anorexia, nausea, vomiting, constipation, obstipation, flatus pattern), urinary symptoms (eg, urgency, frequency, hematuria, or dysuria), and signs of infection (eg, fever, chills). The patient should be questioned about her medical history and any previous surgery.

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Table 15.1 Differential Diagnosis of Acute Pelvic Pain
<i>Gynecologic Disease or Dysfunction</i>
<i>Acute Pain</i>
1. Complication of pregnancy
a. Ectopic pregnancy
b. Abortion, threatened or incomplete
2. Acute infections
a. Endometritis
b. Pelvic inflammatory disease (acute PID) or salpingo-oophoritis
c. Tubo-ovarian abscess
3. Adnexal disorders
a. Hemorrhagic functional ovarian cyst
b. Torsion of adnexa
c. Rupture of functional, neoplastic, or inflammatory ovarian cyst
<i>Recurrent Pelvic Pain</i>
1. Mittelschmerz (midcycle pain)
2. Primary dysmenorrhea
3. Secondary dysmenorrhea
<i>Gastrointestinal</i>
1. Gastroenteritis
2. Appendicitis
3. Bowel obstruction
4. Diverticulitis
5. Inflammatory bowel disease
6. Irritable bowel syndrome
<i>Genitourinary</i>
1. Cystitis
2. Pyelonephritis
3. Ureteral lithiasis
<i>Musculoskeletal</i>
1. Abdominal wall hematoma
2. Hernia
<i>Other</i>

1. Acute porphyria
2. Pelvic thrombophlebitis
3. Aortic aneurysm
4. Abdominal angina

<i>Organ</i>	<i>Spinal Segments</i>	<i>Nerves</i>
<i>Abdominal wall</i>	T12–L1	Iliohypogastric, ilioinguinal, genitofemoral
<i>Lower abdominal wall, anterior vulva, urethra, and clitoris</i>	L1–L2	Ilioinguinal, genitofemoral
<i>Lower back</i>	L1–L2	
<i>Pelvic floor, anus, perineum, and lower vagina</i>	S2–S4	Pudendal, inguinal, genitofemoral, posterofemoral cutaneous
<i>Upper vagina, cervix, uterine corpus, inner third of fallopian tube, broad ligament, upper bladder, terminal ileum, and terminal large bowel</i>	T11–L2 S2–S4	Thoracolumbar autonomics (sympathetics) via hypogastric plexus; sacral autonomics (parasympathetics) via pelvic nerve
<i>Ovaries, outer two thirds of fallopian tubes, and upper ureter</i>	T9–T10	Thoracic autonomics (sympathetics) via renal and aortic plexus and celiac and mesenteric ganglia, aortic and superior mesenteric plexuses

Reprinted from **Rapkin AJ, Howe CN**. Chronic pelvic pain. In: **Boswell MV, Cole BE**, eds. *Weiner's pain management: a practical guide for clinicians*. 7th ed. London, England: Taylor Francis, 2005.

Reproductive Tract

Abnormal Pregnancy

An ectopic pregnancy is defined as implantation of the fetus in a site other than the uterine cavity (15,16,17,18,19,20). The diagnosis and treatment of ectopic pregnancy is discussed in Chapter 18 (21,22,23,24,25,26,27).

Symptoms

Implantation of the fetus in the fallopian tube produces pain only with acute dilation of the tube. If tubal rupture occurs, localized abdominal pain tends to be temporarily relieved and is replaced by generalized pelvic and abdominal pain as the hemoperitoneum develops. A period of amenorrhea followed by bleeding and pain compose the classic triad of symptoms. A mass in the cul-de-sac may produce an urge to defecate. Referred pain to the right shoulder often develops if the intraabdominal blood collection transverses the right colic gutter and irritates the diaphragm (C-3 to C-5 innervation).

Signs

Abdominal examination is usually notable for tenderness and guarding in one or both

lower quadrants. With the development of hemoperitoneum, generalized abdominal distention and rebound tenderness are prominent, and bowel sounds are often decreased. Pelvic examination generally reveals mild tenderness on motion of the cervix. Adnexal tenderness is usually more pronounced on the side of the ectopic pregnancy.

Leaking or Ruptured Ovarian Cyst

Functional cysts (e.g., follicle, corpus luteum) are the most common ovarian cysts and rupture more readily than do benign or malignant neoplasms. The pain associated with rupture of the ovarian follicle at the time of ovulation is called *mittelschmerz*. The

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small amount of blood leaking into the peritoneal cavity and high concentration of follicular fluid prostaglandins could cause this midcycle pelvic pain. However, the pain is mild or moderate and self-limited, and with an intact coagulation system, hemoperitoneum is unlikely. A hemorrhagic corpus luteum cyst can develop in the luteal phase of the menstrual cycle. Rupture of this cyst can produce either a small amount of intraperitoneal bleeding or frank hemorrhage resulting in significant blood loss and hemoperitoneum.

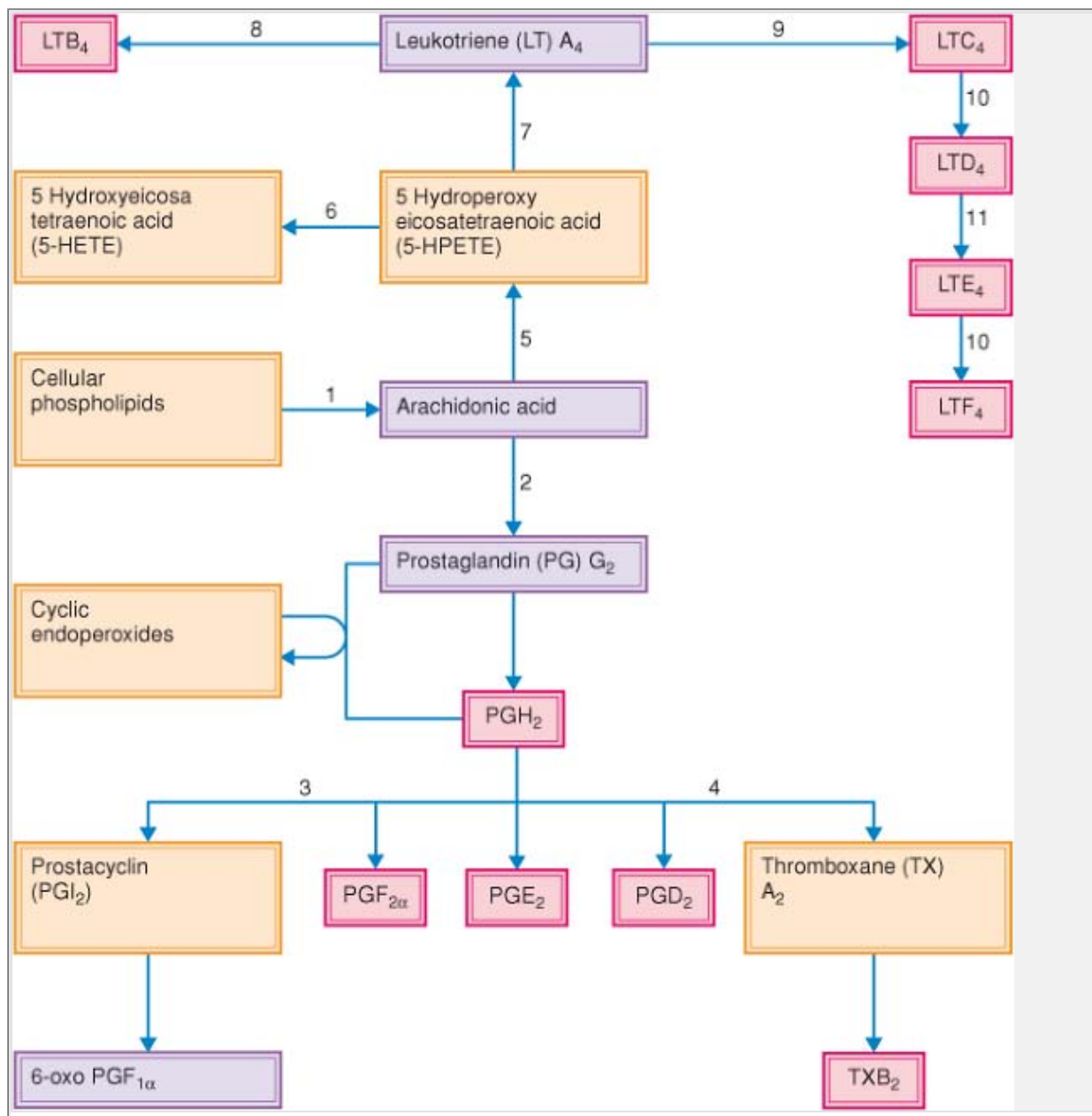


Figure 15.1 The biosynthesis and metabolism of prostaglandins and thromboxane derived from arachidonic acid. (From **Chaudhuri G.** Physiologic aspects of prostaglandins and leukotrienes. *Semin Reprod Endocrinol* 1985;3:219, with permission.)

Nonmalignant neoplasms, most commonly cystic teratomas (dermoid cysts) or cystadenomas, as well as inflammatory ovarian masses, such as endometriomas, can also leak or rupture. A history of a dermoid cyst or endometrioma that has not yet undergone surgical extirpation is not uncommon. **Surgical exploration is indicated if rupture of the cyst leads to hemoperitoneum (corpus luteum) or chemical peritonitis (endometrioma, benign cyst teratoma), which could impair future fertility.**

Symptoms

An ovarian cyst that is not undergoing torsion, rapidly expanding, infected, or leaking does not cause acute pain. **A corpus luteum cyst is the most common cyst to rupture and**

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lead to hemoperitoneum. Symptoms of a ruptured corpus luteum cyst are similar to those of a ruptured ectopic pregnancy. The onset of pain is usually sudden and is associated with increasing generalized abdominal pain and occasionally dizziness or syncope if a hemoperitoneum develops. A ruptured endometrioma or benign cystic teratoma (dermoid cyst) produces similar symptoms; however, dizziness and signs of hypovolemia are not present because blood loss is minimal.

Signs

Hypovolemia is present only when there is a hemoperitoneum. **The most important sign is the presence of significant abdominal tenderness, often associated with rebound tenderness because of peritoneal irritation.** The abdomen can be moderately distended with decreased bowel sounds. On pelvic examination, a mass is often palpable if the cyst is leaking and not completely ruptured. Fever and leukocytosis are rare. The hematocrit is decreased only if active bleeding is present.

Diagnosis

The diagnosis of a ruptured cyst is confirmed by pregnancy test, complete blood count, and ultrasound or culdocentesis. If orthostasis is not present and the peripheral hematocrit levels are relatively normal, a hematocrit of 16% or less of the fluid obtained from the cul-de-sac is usually consistent with leakage of a small amount of blood into the peritoneal fluid and not a hemoperitoneum.

Management

Orthostasis, anemia, or hematocrit of the culdocentesis fluid of greater than 16% suggests hemoperitoneum and usually requires surgical treatment by laparoscopy or laparotomy. Culdocentesis is very helpful in determining the cause of peritonitis: fresh blood suggests a corpus luteum; chocolate "old" blood, an endometrioma; oily sebaceous fluid, a benign teratoma; purulent fluid, pelvic inflammatory disease (PID) or tubo-ovarian abscess. Patients who are not orthostatic or anemic and who have a small amount of blood in the cul-de-sac fluid (culdocentesis fluid hematocrit less than 16%) can often be observed in the hospital, without surgical intervention, or even discharged home from the emergency room after observation.

Torsion of Adnexa

Torsion (twisting) of the vascular pedicle of an ovary, fallopian tube, paratubal cyst, or rarely just a fallopian tube results in ischemia and rapid onset of acute pelvic pain.

A benign cystic teratoma is the most common neoplasm to undergo torsion. Because of adhesions, ovarian carcinoma and inflammatory masses rarely are affected by torsion (28). It is also unusual for a normal tube and ovary to torque, although a polycystic ovary can undergo torsion.

Symptoms

The pain of torsion can be severe and constant or, if the torsion is partial and intermittently untwists, intermittent. The onset of the torsion and the symptoms of abdominal pain frequently coincide with lifting, exercise, or intercourse. Autonomic reflex responses are usually present (e.g., nausea, emesis, apprehension).

Signs

On examination, the abdomen is very tender, and localized rebound tenderness can be noted in the lower quadrants. The most important sign is the presence of a large pelvic mass on physical examination. Mild temperature elevation and leukocytosis may accompany the

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infarction. The diagnosis must be suspected in any woman with acute pain and unilateral adnexal mass.

Diagnosis

The process of torsion occludes the lymphatic and venous drainage of the involved adnexa; therefore, the mass rapidly increases in size and can be palpated on examination or visualized by ultrasound. Ultrasound confirms the presence of a mass.

Management

Adnexal torsion must be treated surgically. If the tissue has not infarcted, the adnexa may be untwisted and a cystectomy performed if appropriate. If necrosis has occurred, an oophorectomy was indicated previously. Now, even with a necrotic-appearing ovary, there is evidence that sparing the adnexa can preserve the ovarian hormonal and reproductive function (28,29). Treatment may be accomplished by laparoscopy or laparotomy, depending on the size of the mass.

Acute Salpingo-oophoritis

The management of acute salpingo-oophoritis and PID are discussed in Chapter 16 (30,31,32,33,34,35).

Symptoms

Gonococcal PID is manifested by the acute onset of pelvic pain that increases with movement, fever, purulent vaginal discharge, and sometimes nausea and vomiting. The pain is often associated with a menstrual period, a time when pathogens have ready access to the upper genital tract. Chlamydial salpingo-oophoritis is associated with more insidious symptoms, which can be confused with the symptoms of irritable bowel syndrome.

Signs

Direct and rebound abdominal tenderness with palpation are usually notable on examination. **The most important signs of acute salpingo-oophoritis are cervical motion tenderness and bilateral adnexal tenderness.** Evaluation of the pelvis may be difficult because of acute pain, but lack of a discrete mass or masses differentiates acute salpingo-oophoritis from tuboovarian abscess or torsion. Often present is leukocytosis, or at least an elevated erythrocyte sedimentation rate (ESR), a nonspecific, although more sensitive, sign of inflammation.

Diagnosis

Other origins of pelvic pain such as appendicitis can be mistaken for PID. Laparoscopy can be used to diagnose salpingitis and rule out other causes of pelvic pain; however, it cannot be used for the diagnosis of endometritis, which is usually based on clinical findings.

Tubo-ovarian Abscess

Tubo-ovarian abscesses, a sequela of acute salpingitis, are usually bilateral, but unilateral abscess formation can occur. The symptoms and signs are similar to those of acute salpingitis, although pain and fever have often been present for longer than 1 week before presentation to the emergency room. A ruptured tubo-ovarian abscess is a life-threatening surgical emergency because gram-negative endotoxic shock can develop rapidly.

Signs

Tubo-ovarian abscesses can be palpated on bimanual examination as very firm, exquisitely tender, bilateral fixed masses. The abscesses can be palpated or "point" in the pelvic cul-de-sac.

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Diagnosis

The clinical diagnosis of tubo-ovarian abscess can be substantiated by ultrasonography. The differential diagnosis of a unilateral mass includes not only tubo-ovarian abscess but also adnexal torsion, endometrioma, leaking ovarian cyst, and periappendiceal or diverticular abscess. If physical and ultrasound examination results are not definitive, laparoscopy or laparotomy must be performed.

Management

A ruptured tubo-ovarian abscess rapidly leads to diffuse peritonitis evidenced by tachycardia and rebound tenderness in all four quadrants of the abdomen. If the abscess is progressive, hypotension and oliguria ensue, making exploratory laparotomy with resection of infected tissue mandatory (35,36,37) (see Chapter 16).

Uterine Leiomyomas

Leiomyomas are uterine smooth muscle tumors (see Chapter 14). Discomfort may be present when myomas are intramural, fundal, or encroaching on adjacent bladder, rectum, or supporting ligaments of the uterus. Acute pelvic pain attributable to uterine leiomyomas is rare, however (38). The pain is usually reported as dyspareunia, dysmenorrhea, or noncyclic pelvic pain. However, a recent study showed that **fibroids are more likely to cause**

dyspareunia and noncyclic pelvic pain than dysmenorrhea. The same study did not find an association between worsening pain with increased fibroid volume or number.

Acute pelvic pain can develop if the myoma undergoes degeneration or torsion. Degeneration of myomas occur secondary to loss of blood supply, usually attributable to rapid growth associated with pregnancy. **In a nonpregnant woman, degenerating uterine leiomyoma often is misdiagnosed, frequently being confused with subacute salpingo-oophoritis.** A pedunculated subserosal leiomyoma can undergo torsion ischemic necrosis; when this situation occurs, it is associated with pain similar to that of adnexal torsion. When a submucous leiomyoma becomes pedunculated, the uterus contracts force-fully as if to expel a foreign body, and the resulting pain is similar to that of labor. The cramping pain is usually associated with hemorrhage.

Signs

Abdominal examination reveals an irregular solid mass or masses arising from the uterus. If degeneration occurs, the inflammation can cause abdominal tenderness in response to palpation and mild localized rebound tenderness. Elevation of temperature and leukocytosis also can occur.

Diagnosis and Management

Ultrasound is useful in distinguishing adnexal from uterine etiology of an eccentric mass. However, if fever is present, it is important to rule out tubo-ovarian abscess. Degeneration of a leiomyoma is treated with observation and pain medication. A pedunculated, torqued, subserosal leiomyoma can easily be excised laparoscopically; however, surgery is not mandatory. A submucous leiomyoma with pain and hemorrhage should be excised transcervically, with hysteroscopic guidance if needed.

Endometriosis

Women with endometriosis often experience dysmenorrhea, dyspareunia, and dyschezia. These women often have a history of luteal phase bleeding or infertility. Acute pain attributable to endometriosis is usually premenstrual and menstrual; however, if nonmenstrual acute generalized pain occurs, a ruptured endometrioma (chocolate endometriotic cyst within the ovary) should be considered.

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The management of endometriosis is discussed in Chapter 29.

Diagnosis

The abdomen is often tender in the lower quadrants. Significant distention or rebound tenderness is usually not present. Pelvic examination often reveals a fixed, retroverted uterus with tender nodules in the uterosacral region or thickening of the cul-de-sac. An adnexal mass, if present, usually is fixed to the broad ligament and cul-de-sac. In a patient who has an established diagnosis of endometriosis or who has recently been treated surgically for the disease, a trial of ovarian hormonal suppression (pseudomenopause) can be used to treat the condition and to confirm the correlation between the current pain and the underlying diagnosis of endometriosis.

Gastrointestinal Tract

Appendicitis

The most common intestinal source of acute pelvic pain in women is appendicitis. Lifetime incidence in the United States is 7%, and it is the most common cause of emergent abdominal surgery (39). The symptoms and signs of appendicitis can be similar to those of PID. The first symptom of appendicitis is typically diffuse abdominal pain, especially periumbilical pain, followed by anorexia, nausea, and vomiting. Within a matter of hours, the pain generally shifts to the right lower quadrant. Fever, chills, emesis, and obstipation may ensue. However, this classic symptom pattern is often absent. Atypical abdominal pain can occur when the appendix is retrocecal or entirely within the true pelvis (which occurs in 15% of the population) (39). In this setting, tenesmus and diffuse supra-pubic pain may occur. The patient with appendicitis is more likely to have pronounced and persistent gastrointestinal symptoms than the patient with salpingo-oophoritis.

Signs

Local tenderness is usually elicited on palpation of the right lower quadrant (McBurney point). The appearance of severe generalized muscle guarding, abdominal rigidity, rebound tenderness, right-sided mass, tenderness on rectal examination, positive psoas sign (pain with forced hip flexion or passive extension of hip), and obturator signs (pain with passive internal rotation of flexed thigh) indicates appendicitis. A low-grade fever is generally present, but the temperature may be normal. High temperatures are typically seen with appendiceal perforation. The pelvic examination usually does not disclose cervical motion or bilateral adnexal tenderness, but right-sided unilateral adnexal tenderness can be present.

Diagnosis

Many patients with acute appendicitis have normal total leukocyte counts; however, a left shift is usually revealed in the evaluation. Findings of ultrasound examination of the pelvic organs generally are normal, whereas the appendix may appear abnormal on ultrasound or computed tomography (CT). Gastrografin barium enema, or CT with contrast with normal filling of the appendix rules out appendicitis. Diagnostic laparoscopy can be useful to rule out other sources of pelvic pathology, but it is occasionally difficult to visualize the appendix sufficiently to rule out early appendiceal inflammation.

Management

Initial management is intravenous administration of fluids, strict restriction of any oral intake, and preoperative antibiotics followed by laparoscopy or laparotomy. **Laparotomy has a false-positive rate of 20%, making it an acceptable approach, and is preferable**

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to continued observation with the risk of eventual rupture and peritonitis. Not only is a ruptured appendix life threatening, but it also may have profound sequelae for the fertility of a woman of reproductive age.

Acute Diverticulitis

Acute diverticulitis is a condition in which there is inflammation of a diverticulum or outpouching of the wall of the colon, usually involving the sigmoid colon. Diverticulitis typically affects postmenopausal women but can occur in women in their 30s and 40s.

Symptoms

The severe, left lower quadrant pain of diverticulitis can occur following a long history of symptoms of irritable bowel (bloating, constipation, and diarrhea), although diverticulosis usually is asymptomatic. Diverticulitis is less likely to lead to perforation and peritonitis than is appendicitis. Fever, chills, and constipation typically are present, but anorexia and vomiting are uncommon.

Signs

Abdominal examination reveals distention with left lower quadrant tenderness on direct palpation and localized rebound tenderness. Abdominal and pelvic examination may reveal a poorly mobile, doughy inflammatory mass in the left lower quadrant. Bowel sounds are hypoactive, whereas they are absent with peritonitis. Leukocytosis frequently is observed.

Diagnosis and Management

Computed axial tomography is a useful adjunct to history and physical examination. It will reveal a swollen, edematous bowel and can rule out an abscess. A barium enema is contraindicated. Diverticulitis is initially managed medically with intravenous administration of fluids, strict restriction of oral intake, and broad-spectrum intravenous antibiotics. A diverticular abscess, obstruction, fistula, or free perforation requires surgical intervention.

Intestinal Obstruction

The most common causes of intestinal obstruction in women are postsurgical adhesions, hernia formation, inflammatory bowel disease, and carcinoma of the bowel or ovary.

Symptoms

Intestinal obstruction is heralded by the onset of colicky abdominal pain followed by abdominal distention, vomiting, constipation, and obstipation. Higher and more acute obstruction results in early vomiting, whereas colonic obstruction presents with a greater degree of abdominal distention and obstipation. Vomiting first consists of gastric contents, followed by bile, then material with feculent odor, depending on the level of obstruction.

Signs

Marked abdominal distention is present with abdominal obstruction. At the onset of mechanical obstruction, bowel sounds are high pitched and maximal during an episode of colicky pain. As the obstruction progresses, bowel sounds decrease and, when absent, suggest ischemic bowel. Elevated white blood cell (WBC) count and fever often are present in the late stages.

Diagnosis and Management

An upright abdominal x-ray series shows a characteristic gas pattern, distended loops of bowel, and air fluid levels; and it helps to determine whether obstruction is partial or complete (no colonic gas seen). Complete obstruction requires surgical management, whereas partial

obstruction often can be managed with intravenous fluids and nasogastric suction. The cause of the obstruction should be determined and treated if possible.

Urinary Tract

Ureteral colic that is due to ureteral lithiasis is caused by a sudden increase in intraluminal pressure and associated inflammation. Urinary tract infections producing acute pain include cystitis and pyelonephritis. The most common microbes causing urinary tract infections are *E. coli* followed by *Proteus*, *Klebsiella*, and *Pseudomonas*.

Symptoms and Signs

The pain of lithiasis is typically severe and crampy; it can radiate from the costovertebral angle to the groin. Hematuria is often present. Cystitis is associated with dull suprapubic pain, urinary frequency, urgency, dysuria, and occasionally hematuria. Because urethritis can occur secondary to chlamydia or gonorrhea and has similar symptoms, these infections must be ruled out if appropriate. Pyelonephritis is associated with flank and costovertebral angle pain, although lateralizing lower abdominal pain occasionally is present. There is pain with firm pressure over the costovertebral angle in the case of lithiasis or pyelonephritis. Peritoneal signs are absent. Suprapubic tenderness may accompany cystitis.

Diagnosis

Diagnosis of stone is afforded by urinalysis revealing red blood cells and outlining the stone using ultrasound or CT urography or intravenous pyelography (uric acid stones may not be detected by CT). The diagnosis of urinary tract infection is based on urinalysis revealing bacteria and leukocytes (10 WBCs /high-power field) and subsequently confirmed by culture.

Management

Expectant medical treatment consists of intravenous administration of fluids or oral hydration and pain control. Surgical management, such as lithotripsy or open surgery, also is an option for renal lithiasis. Nonpregnant women (and pregnant women who are afebrile with a normal WBC count) with pyelonephritis and all women with cystitis can be treated on an outpatient basis. Nonpregnant women can be treated with a 14-day course of a *fluoroquinolone* or *trimethoprim/sulfamethoxazole* (some recommend one intravenous dose of a third-generation cephalosporin before discharging patients with oral antibiotics) (see Chapter 16) (40,41,42,43). It is important to follow up urine culture sensitivities and treat accordingly. If there is no improvement or if any immunocompromising conditions are present such as HIV, intravenous drug use/abuse, diabetes, pregnancy, or chronic steroid use, the patient should be hospitalized and given intravenous antibiotics.

Tuberculosis should be excluded as a cause of pyelonephritis if the characteristic hematuria with sterile pyuria is present and the patient's condition does not improve with antibiotics.

Diagnostic Tools for

All women of reproductive age with acute pelvic pain should have a complete blood count with differential, ESR, urinalysis, and a sensitive qualitative urine or serum Acute Pelvic Pain pregnancy test. The sedimentation rate is nonspecific but often is the only abnormal

laboratory finding in women with subacute PID. Other studies that may be helpful include pelvic ultrasound, culdocentesis with hematocrit if bloody fluid is obtained, and Gram stain with culture if the fluid is purulent. The presence of a mass in the cul-de-sac precludes culdocentesis. Pelvic ultrasound is useful to rule out ectopic gestation or to assess the adnexae if the results of the examination are confusing or difficult to interpret because of obesity or guarding. Abdominal x-ray series or upper or lower Gastrografin studies are helpful to rule out gastrointestinal pathology when gastrointestinal symptoms predominate. Computed tomography scan is useful for evaluation of retroperitoneal masses or abscesses related to the gastrointestinal tract.

Diagnostic laparoscopy is reserved for establishing the diagnosis in patients who have acute abdomen of uncertain cause, for elucidating the nature of an ambiguous adnexal mass, or for delineating whether a pregnancy is intrauterine or extrauterine (if ultrasound results are negative or equivocal). If there is clinical evidence of salpingo-oophoritis, diagnostic laparoscopy can be used to confirm the diagnosis. Visualization is hampered if diagnostic laparoscopy is performed for a large pelvic mass (12 cm) and is relatively contraindicated in patients with peritonitis, severe ileus, or bowel obstruction. In these settings, laparotomy is preferable.

Cyclic Pain: Primary and Secondary Dysmenorrhea

Dysmenorrhea is a common gynecologic disorder affecting as many as 50% of menstruating women (11). Primary dysmenorrhea refers to menstrual pain without pelvic pathology, whereas secondary dysmenorrhea is defined as painful menses associated with underlying pathology. Primary dysmenorrhea usually appears within 1 to 2 years of menarche, when ovulatory cycles are established. The disorder affects younger women but may persist into the 40s. Secondary dysmenorrhea usually develops years after menarche and can occur with anovulatory cycles. The differential diagnosis of secondary dysmenorrhea is outlined in Table 15.3 (2).

Primary Dysmenorrhea

The cause of primary dysmenorrhea is increased endometrial prostaglandin production (44,45,46,47,48). These compounds are found in higher concentrations in secretory endometrium than in proliferative endometrium. The decline of progesterone levels in the late luteal phase triggers lytic enzymatic action, resulting in a release of phospholipids with the generation of arachidonic acid and activation of the cyclooxygenase (COX) pathway. The biosynthesis and metabolism of prostaglandins and thromboxane derived from arachidonic acid are depicted in Fig. 15.1 (46). Increased synthesis of prostanoids in women with primary dysmenorrhea results in higher uterine tone with high-amplitude contractions causing dysmenorrhea (47,48,49). It is theorized that women suffering from dysmenorrhea have upregulated COX enzyme activity and prostanoid synthase activity. This has led to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which act as COX enzyme inhibitors, for therapy (48). In the past it was shown that vasopressin concentrations are also higher in women with dysmenorrhea (49). However, a more current study did not show vasopressin elevations and purported that treatment with a vasopressin antagonist, *atosiban*, had no effect on dysmenorrhea (50).

Symptoms

The pain of primary dysmenorrhea usually begins a few hours before or just after the onset of a menstrual period and may last 48 to 72 hours. The pain is similar to labor,

with suprapubic cramping, and may be accompanied by lumbosacral backache,

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pain radiating down the anterior thigh, nausea, vomiting, diarrhea, and rarely syncopal episodes. The pain of dysmenorrhea is colicky in nature and, unlike abdominal pain that is due to chemical or infectious peritonitis, is relieved by abdominal massage, counter-pressure, or movement of the body.

Table 15.3 Differential Diagnosis of Chronic Pelvic Pain

<i>Gynecologic</i>	<i>Genitourinary</i>
<i>Non-cyclic</i>	Recurrent or relapsing cystourethritis
Adhesions	Urethral syndrome
Endometriosis	Interstitial cystitis
Salpingo-oophoritis	Ureteral diverticuli or polyps
Ovarian remnant or retained ovary syndrome	Carcinoma of the bladder
Pelvic congestion	Ureteral obstruction
Ovarian neoplasm benign or malignant	Pelvic kidney
Pelvic relaxation	<i>Neurologic</i>
<i>Cyclic</i>	Nerve entrapment syndrome, neuroma, or other neuropathies
Primary dysmenorrhea	Trigger points
Mittelschmerz	<i>Musculoskeletal</i>
Secondary dysmenorrhea	<i>Low-back-pain syndrome</i>
Endometriosis	Congenital anomalies
Uterine or vaginal anomalies with obstruction of menstrual outflow	Scoliosis and kyphosis
Intrauterine synechiae (Asherman's syndrome)	Spondylolysis
Endometrial polyps or intrauterine device (IUD)	Spondylolisthesis
Uterine leiomyomata	Spinal injuries
Adenomyosis	Inflammation
Pelvic congestin syndrome	Tumors
Atypical cyclic	Osteoporosis
Endometriosis	Degenerative changes
Adenomyosis	Coccydynia
Ovarian remnant syndrome	Myofascial syndrome
Chronic functional cyst formation	Hernia
<i>Gastrointestinal</i>	<i>Systemic</i>
Irritable bowel syndrome	Fibromyalgia
Ulcerative colitis	Acute intermittent porphyria
Granulomatous colitis (Crohn's disease)	Abdominal migraine
Carcinoma	Connective tissue disease including systemic lupus erythematosus
Infection	Lymphoma

Recurrent partial bowel obstruction	Neurofibromatosis
Diverticulitis	
Hernia	
Abdominal angina	
Recurrent appendiceal colic	

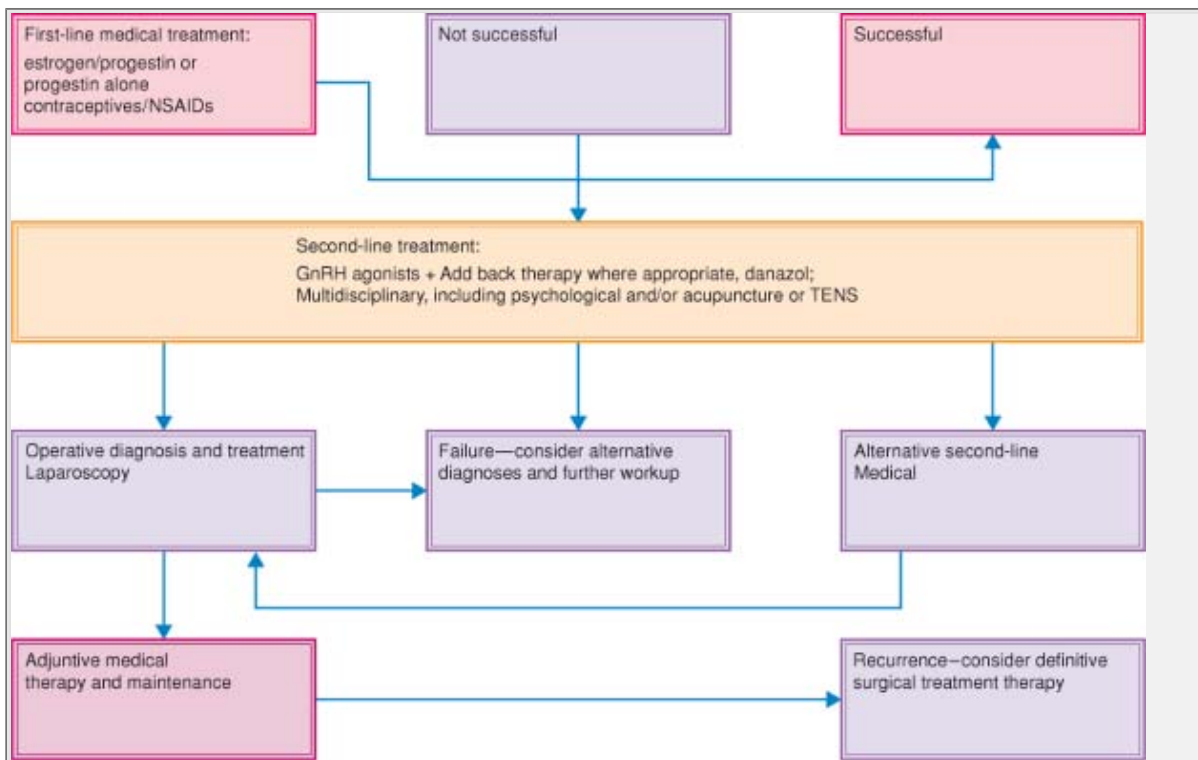


Figure 15.2 Endometriosis (suspected)/cyclic pelvic pain treatment. NSAIDs, nonsteroidal anti-inflammatory drugs; GnRH, gonadotropin-releasing hormone; TENS, transcutaneous electrical nerve stimulation. (From **Rapkin AJ, Howe CN.** Chronic pelvic pain: a review. In: *Family practice recertification*. Monroe Township, New Jersey: Medical World Communications, 2006;28: 59–67.)

Signs

On examination, the vital signs are normal. The suprapubic region may be tender to palpation. Bowel sounds are normal, and there is no upper abdominal tenderness and no abdominal rebound tenderness. **Bimanual examination at the time of the dysmenorrheic episode often reveals uterine tenderness; however, severe pain does not occur with movement of the cervix or palpation of the adnexal structures.** The pelvic organs are normal in primary dysmenorrhea.

Diagnosis

To diagnose primary dysmenorrhea, it is necessary to rule out underlying pelvic pathology and confirm the cyclic nature of the pain. The differential diagnosis of secondary dysmenorrhea includes primary dysmenorrhea and noncyclic pelvic pain. Whereas the diagnosis of primary dysmenorrhea is based on history and presence of a normal pelvic examination,

the diagnosis of secondary dysmenorrhea may require review of a pain diary and an ultrasound examination or laparoscopy or hysteroscopy or both. During the pelvic examination,

the size, shape, and mobility of the uterus; the size and tenderness of adnexal structures; and the nodularity or fibrosis of uterosacral ligaments or rectovaginal septum should be assessed. Cervical studies for gonorrhea and chlamydia and, if relevant, a complete blood count with an ESR, are helpful to rule out subacute salpingo-oophoritis. If no abnormalities are found, a tentative diagnosis of primary dysmenorrhea can be established.

Treatment

Prostaglandin synthase inhibitors, or NSAIDs, are effective for the treatment of primary dysmenorrhea (51). The inhibitors should be taken before or at the onset of pain and then continuously every 6 to 8 hours to prevent reformation of prostaglandin by-products. The medication should be taken for the first few days of menstrual flow. A 4- to 6-month course of therapy is warranted to determine whether the patient will respond to treatment. Changes in dosages and types of inhibitors should be attempted if initial treatment is not successful. The medication may be contraindicated in patients with gastrointestinal ulcers or bronchospastic hypersensitivity to aspirin. Side effects are usually mild and include nausea, dyspepsia, diarrhea, and occasionally fatigue.

Leukotrienes have been found to mediate inflammation within the uterus and, in addition to prostaglandins, contribute to dysmenorrhea. For patients who fail to respond to NSAIDs, leukotriene receptor antagonists, commonly used to treat asthma, are potential therapeutic agents (52).

For patients with primary dysmenorrhea who have no contraindications to hormonal contraceptive agents (such as oral combined or progesterone only, either cyclic or continuous, transdermal, vaginal ring, injectable preparations, or intrauterine devices) and who desires contraception, oral contraceptives are more effective than placebo alone and resulted in less absence from work or school in one review (53). Hormonal contraceptives inhibit ovulation, decrease endometrial proliferation, and create an endocrine milieu similar to the early proliferative phase of the menstrual cycle, when prostaglandin levels are lowest. Decreased prostaglandin levels result in less uterine cramping. If the patient does not respond to this regimen, *hydrocodone* or *codeine* may be added for 2 to 3 days per month; however, before addition of the narcotic medication, psychological factors should be evaluated, and other organic pathology should be ruled out with diagnostic laparoscopy.

Nonpharmacologic pain management, in particular acupuncture or transcutaneous electrical nerve stimulation (TENS), may also be useful (54,55). Acupuncture is thought to excite receptors or nerve fibers, blocking pain impulses through interactions with mediators like serotonin and endorphins (55). It has been found to be effective for treating dysmenorrhea in a few small studies (54,55). The body's perception of pain signals is altered with TENS. It does not directly affect uterine contractions (55). In one study of women with primary dysmenorrhea undergoing TENS, 30% reported marked pain relief, 60% moderate pain relief, and 10% no relief (56). It appears that TENS is more effective for pain relief at high frequency than at low frequency (55).

Another alternative method of treatment is spinal manipulation. In clinical trials, however, it has not been found to be effective (57,58). Methods used only rarely to treat primary dysmenorrhea include surgical laparoscopic uterine nerve ablation and presacral neurectomy.

Secondary Dysmenorrhea

Second dysmenorrhea is cyclic menstrual pain that occurs in association with underlying dysmenorrhea lying pelvic pathology. It usually occurs years after the onset of menarche,

but the definition does not reflect age of onset. **The pain of secondary dysmenorrhea often begins**

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1 to 2 weeks before menstrual flow and persists until a few days after the cessation of bleeding. The mechanisms underlying secondary dysmenorrhea are diverse and not fully elucidated, although most involve either excess prostaglandin production or hypertonic uterine contractions secondary to cervical obstruction, intrauterine mass, or the presence of a foreign body. However, NSAIDs and hormonal contraceptives are less likely to provide pain relief in women with secondary dysmenorrhea than in those with primary dysmenorrhea. The most common cause of secondary dysmenorrhea is endometriosis, followed by adenomyosis and intrauterine device (for a discussion of endometriosis, see diagnosis of acute and chronic pain, this chapter and Chapter 29). The differential diagnosis of secondary dysmenorrhea is outlined in Table 15.3. The management of secondary dysmenorrhea is treatment of the underlying disorder (Fig. 15.2).

Table 15.4 Rome II Criteria for Diagnosis of Irritable Bowel Syndrome

At least 12 weeks, which are not necessarily consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features:

1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool.

Reprinted from **Rapkin AJ, Howe CN.** Chronic pelvic pain: a review. In: *Family practice recertification*. Monroe Township, New Jersey: Medical World Communications, 2006.

Adenomyosis

Adenomyosis is defined as presence of endometrial tissue within the myometrium, at least 1 high-power field from the basis of the endometrium, whereas endometriosis is characterized by ectopic endometrium appearing within the peritoneal cavity. Adenomyosis, endometriosis, and uterine leiomyomas frequently coexist. Although occasionally noted in women in their younger reproductive years, the average age of symptomatic women is usually older than 40 years. Increasing parity may be a risk factor according to one study (59,60).

Symptoms

Adenomyosis often is asymptomatic. Symptoms typically associated with adenomyosis include excessively heavy or prolonged menstrual bleeding, dyspareunia, dyschezia, and dysmenorrhea. Symptoms often begin up to a week before the onset of a menstrual flow and may not resolve until after the cessation of menses.

Signs

The uterus is diffusely enlarged, although usually less than 14 cm in size, and is often soft and tender, particularly at the time of menses. Mobility of the uterus is not restricted, and there is no associated adnexal pathology.

Diagnosis

Adenomyosis is a clinical diagnosis and can be confirmed only by pathology review. Imaging studies, although helpful, are not definitive. Because of their cost and negligible improvement in diagnostic accuracy, these studies are not recommended routinely. In women with diffuse uterine enlargement and a negative pregnancy test results, secondary dysmenorrhea may be attributed to adenomyosis; however, the pathologic confirmation of suspected adenomyosis can be made only at the time of hysterectomy. In one study to confirm preoperative diagnosis of adenomyosis before hysterectomy, the clinical diagnosis of adenomyosis was confirmed in only 48% of the cases (26).

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Management

The management of adenomyosis depends on the patient's age and desire for future fertility. Relief of secondary dysmenorrhea caused by adenomyosis can be ensured after hysterectomy, but less invasive approaches can be tried initially. Nonsteroidal antiinflammatory agents, oral contraceptives, and menstrual suppression using progestins have all been found to be useful. Treatment follows the same protocol as treatment for endometriosis.

Chronic Pelvic Pain

Chronic pelvic pain remains an inclusive, general diagnosis that encompasses many more specific causes, from endometriosis to nerve entrapment syndrome. Various forms of chronic pelvic pain affect 12% to 20% of women in the United States (61,62). The differential diagnosis of chronic pelvic pain is outlined in Table 15.3.

Patients with chronic pelvic pain are frequently anxious and depressed. Their marital, social, and occupational lives have usually been disrupted. These patients have often had poor treatment outcomes after traditionally effective gynecologic and medical therapy and may have undergone multiple unsuccessful surgical procedures for pain. About 12% to 19% of hysterectomies are performed for pelvic pain, and 30% of patients who present to pain clinics have already had a hysterectomy (63,64). **Approximately 60% to 80% of patients undergoing laparoscopy for chronic pelvic pain have no intraperitoneal pathology, nor do they have tissue distortion that correlates with the pain (2). Additionally, the relationship between the pain response and certain types of prevalent intraperitoneal pathology, such as endometriosis, adhesions, or venous congestion, can be inconsistent. Nongynecologic causes of pain, such as irritable bowel syndrome, interstitial cystitis, abdominal wall or pelvic floor myofascial syndrome, or neuropathy, are frequently overlooked but common causes of chronic pelvic pain.**

Recent investigations have suggested that "plasticity" of the nervous system or alterations in signal processing may be involved in the maintenance of painful states (2,5,10). Various neurohumoral modulators, such as prostaglandins, vasoactive intestinal peptide, substance P, and endorphins, can modulate peripheral neurotransmission and also affect neurotransmission at the level of the spinal cord (6,65). Chronic exposure to these neuroinflammatory factors can cause adaptive changes within the peripheral and central nervous system that predispose to allodynia and hyperalgesia (6,9,10,11). The spinal cord is not a simple conduit between the periphery and the brain. It is an important site of "gating" mechanisms, such as excitation, inhibition, convergence, and summation of neural stimuli (66). The pain sensation is also modified by neurotransmitters within the brain, such as norepinephrine, serotonin, and -aminobutyric acid (GABA), as well as by endogenous

endorphin and nonendorphin algic systems. Different regions of the brain are also important in altering the sensory and affective components of the pain response. Evidence from animal studies indicates that supraspinal factors can interact at the level of the dorsal horn to modulate the sensory perception of pain from the pelvic viscera (9,67). Overlapping afferent input from nearby viscera can cause a perception of referred pain, making the diagnosis of origin difficult (9). The sensory and affective component of pain is affected by early experience, conditioning, fear, arousal, depression, and anxiety (68).

Evaluation of Chronic

On the first visit, a thorough pain history should be performed, taking into consideration

Pelvic Pain the nature of each pain symptom: location, radiation, severity, aggravating and alleviating factors; effect of menstrual cycle, stress, work, exercise, intercourse, and

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orgasm; the context in which pain arose; and the social and occupational toll of the pain (Table 15.5). A visual analog pain scale listing numbers 0 through 10 and stating "no pain" and "worst possible pain" is helpful in assessing the severity of pain and comparing the changes in severity over subsequent visits (69). The use of a questionnaire is helpful and can help better record and define the patient's symptoms. An outline of a woman's body can be used to help the patient define the location and characteristics of pain experienced (2).

Table 15.5 Pain History Mnemonic

Pain History OLD CAARTS
Onset When and how did pain start? Did it change over time?
Location Localize specifically. Can you put a finger on it?
Duration How long does it last?
Characteristics Cramping, aching, stabbing, burning, "like lightening," tingling, itching
Alleviating/Aggravating factors What makes it better (medication, stress reduction, heat/ice, position change) or worse (specific activity, stress, menstrual cycle)?
Associated symptoms GYN (dyspareunia, dysmenorrhea, abnormal bleeding, discharge, infertility), GI (constipation, diarrhea, bloating, gas, rectal bleeding), GU (frequency, dysuria, urgency, incontinence), NEURO (specific nerve distribution)
Radiation Does it move to other areas (dermatomal distribution)?
Temporal What time of day (elation to menstrual cycle and activities of daily living)?
Severity Scale of 0–10
GYN, gynecological; GI, gastrointestinal; GU, genitourinary; NEURO, neurological. From Rapkin AJ, Howe CN . Chronic pelvic pain: a review. In: <i>Family practice recertification</i> . Monroe Township, New Jersey: Medical World Communications, 2006;28:59–67.

The patient should be questioned about symptoms specific to the types of pathology (see Table 15.3):

- **Genital** (abnormal vaginal bleeding, discharge, dysmenorrhea, dyspareunia, infertility)
- **Enterocoelic** (constipation, diarrhea, flatulence, hematochezia, and relationship of pain and pain relief to bowel movements)
-

Musculoskeletal/neuropathic (trauma, exacerbation with exercise, or postural changes)

Urologic (urgency, frequency, nocturia, dysuria, incontinence, hematuria)

The history should include gynecologic, medical, and surgical factors; medication intake; prior evaluations for pain; and operative and pathology reports (2).

Symptoms of an acute process (fever, anorexia, nausea, emesis, significant diarrhea, hematochezia, obstipation, abdominal distention, undiagnosed uterine bleeding, pregnancy, or recent abortion) should alert the physician to the possibility of an acute condition requiring immediate medical or surgical intervention. This occurrence is especially important if symptoms are accompanied by elevated temperature, orthostasis, peritoneal signs, pelvic or abdominal mass, abnormal complete blood count, positive genital or urinary tract cultures, or a positive pregnancy test result.

A complete physical examination should be performed, with particular attention directed to the abdominal and lumbosacral areas, external genitalia, and internal organs via vaginal,

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bimanual, and rectovaginal examination. **The examination should include the *Carnett test*, which is an evaluation of the abdomen with muscles tensed (head raised off the table or with straight leg raising) to differentiate abdominal wall and visceral sources of pain. Abdominal wall pain is augmented and visceral pain is diminished with these maneuvers (70,71).** While standing, the patient should be examined for hernias, both abdominal (inguinal and femoral) and pelvic (cystocele and enterocele). An attempt should be made to locate by palpation the tissues that reproduce the patient's pain. If abdominal wall sources of pain are noted, it is useful to block these areas with local anesthetics and then perform the pelvic examination (70,71).

The Psychological Component

A pain history includes the current and past psychological history and focuses on psychosocial factors; history of past (or current) physical, sexual, or emotional abuse; history of psychiatric hospitalization; suicide attempts; and chemical dependency (2,72). Many studies have shown that childhood abuse in general and childhood sexual abuse in particular are risk factors for chronic pelvic pain (72).

The attitude of the patient and her family toward the pain, resultant behavior of the patient and her family, and current upheavals in the patient's life should be discussed. The part of the history relating to sensitive issues may have to be revisited after establishing rapport with the patient.

It is vital to appreciate the various influences that can distort pain perception and expression. A distinction can be drawn between factors leading to a painful condition and those now maintaining it. Whatever the original cause of the pain, when pain has persisted for any length of time, it is likely that other factors are now maintaining or at least contributing to it. The full physical evaluation, outlined previously, should be accompanied by a review of psychosocial factors. Pain is commonly accompanied by anxiety and depression, and these conditions need to be carefully assessed and treated (2). In a typical gynecologic setting, referral to a psychologist for parallel evaluation can evoke resistance. The inference is drawn that the referring physician is ascribing the pain to psychological causes. The patient needs to understand the reason for this referral and to be reassured that it is a routine and necessary part of the evaluation.

Gynecologic Causes

The most common gynecologic disorders noted at the time of laparoscopy performed to assess chronic pelvic pain are endometriosis and adhesions. Patients with obvious gynecologic pathology, such as benign or malignant ovarian cysts, uterine leiomyomas of size sufficient to encroach on supporting ligaments or other somatic structures, or significant pelvic relaxation should be evaluated and treated in a manner that is appropriate for the underlying condition (see Chapters 14 and 24). Pain associated with these conditions is generally not severe, and appropriate surgical management is therapeutic.

Endometriosis

A thorough discussion of the management of endometriosis is presented in Chapter 29 (73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101).

Endometriosis can be demonstrated in 15% to 40% of patients undergoing laparoscopy for chronic pelvic pain (73). Endometriosis produces a low-grade inflammatory reaction; over time this results in adhesions between confluent pelvic organs (74,75). However, the cause of the pain is not well established. **There is no correlation between the location of disease and pain symptoms (76,77). There also appears to be no relationship between the incidence or severity of pain and the stage of the endometriotic lesions, and as many as 30% to 50% of patients have no pain regardless of stage. Similarly, 40% to 60% of patients have no tenderness on examination regardless of stage (77).** However, other studies have shown that deeply infiltrating endometriosis lesions that involve the

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rectovaginal septum and the bowel, ureters, and bladder are strongly associated with pain (75,78,79). Vaginal and uterosacral endometrioses are associated with deep dyspareunia (80). Dyspareunia may be caused by pressure on inflamed tissues and neural invasion, in addition to stretching and tearing during intercourse of pelvic structures bound by adhesions.

Prostaglandin E and F₂ production from explants of petechial lesions present in mild, lowstage disease was found to be significantly greater than from the explants of powder-burn or black lesions, which are more common in patients with higher-stage endometriosis (81). Therefore, prostaglandin production may account for severe pain in some patients with mild disease.

Endometriosis is a surgical diagnosis based on identification of characteristic lesions.

Adhesions

Adhesions noted at the time of laparoscopy are often in the same general region of the abdomen as the source of the pelvic pain (102); however, neither the specific location (i.e., adnexa structures, parietal, visceral peritoneum, or bowel) nor density of the adhesions correlates consistently with the presence of pain symptoms (103).

Various studies of adhesiolysis have not consistently demonstrated a significant long-term reduction in pain scores, whereas others show an improvement but one no greater than in the placebo group (laparoscopy without adhesiolysis) (104,105,106,107). In one study of lysis of adhesions, a subgroup of women with anxiety, depression, multiple somatic symptoms, and social and occupational disruption responded poorly to adhesiolysis. The group without these characteristics had significant improvement in pain (104,105). A prospective study, however, noted a significant improvement in pain with two of three methods of assessment only if the adhesions were dense and involved the bowel (108).

Symptoms

Noncyclic abdominal pain, sometimes increased with intercourse or activity, is a common source of pain in women with adhesions, but there is no symptom pattern specific for adhesions. Chronic pelvic pain developing from adhesions is thought to result from restriction of bowel mobility and distention (109). Furthermore, dense adhesions involving bowel can cause partial or complete bowel obstruction.

Signs

The abdominal wall must be carefully evaluated for myofascial or neurological sources of pain. Most women with adhesions have had a prior surgical procedure with possible injury to abdominal wall structures that may be the cause of pain. Decreased mobility of pelvic organs or adnexal enlargement can often be detected in patients with adhesions.

Diagnosis

Diagnostic laparoscopy is recommended if somatic causes are ruled out and the results of the psychological evaluation are negative. Recent advances in microlaparoscopy have enabled the development of a new technique known as "conscious pain mapping," whereby physicians may better locate the specific adhesions associated with pelvic pain using local anesthesia and conscious sedation (110,111). In an observational study of 50 women using local anesthesia, manipulation of appendiceal and pelvic adhesions contributed to pelvic pain (112). Further studies are needed to correlate the lysis of such painful adhesions with pain relief. Thus far, laparoscopic pain mapping has not been shown to improve outcome over traditional laparoscopic therapy (2,14).

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Management

Currently, the causal role of adhesions in the genesis of pelvic pain is uncertain, and lysis is recommended only after thorough multidisciplinary evaluation and in the context of an integrated treatment approach that addresses stress, mood, and associated behavioral responses. Repeated surgical procedures for lysis are not recommended.

Pelvic Congestion

In 1954, Taylor suggested that emotional stress could lead to autonomic nervous system dysfunction manifested as smooth muscle spasm and congestion of the veins draining the ovaries and uterus (113). Transuterine venography in women with chronic pelvic pain often reveals delayed disappearance of contrast medium from the uterine and ovarian veins (114). Considering that pregnant and postpartum women have asymptomatic pelvic congestion, the role of congested veins in the causation of pelvic pain is uncertain. The specific neurotransmitters involved in mediating sympathetic efferent-maintained pain syndrome are unknown.

Signs and Symptoms

Pelvic congestion most commonly affects women of reproductive age. Typical symptoms include bilateral lower abdominal and back pain, secondary dysmenorrhea, dyspareunia, abnormal uterine bleeding, chronic fatigue, and irritable bowel symptoms. Pain usually begins with ovulation and lasts until the end of menses. The uterus is often bulky, and the ovaries

are enlarged with multiple functional cysts. The uterus, parametria, and uterosacral ligaments are tender.

Diagnosis

Transuterine venography has been the primary method for diagnosis, although other modalities, such as pelvic ultrasound, magnetic resonance imaging, and laparoscopy, may disclose varicosities (115). Because of the cost and possible side effects of treatment, further management should be based on related symptoms and not simply on the presence of varicosities.

Management

Treatment of suspected pelvic congestion ranges from the less invasive hormonal suppression and cognitive behavioral pain management to the more invasive ovarian vein embolization or hysterectomy and salingo-ovariectomy. Low-estrogen, progestin-dominant continuous oral contraceptives, high-dose progestins, and gonadotropin-releasing hormone (GnRH) analogues often provide pain relief (116,117). Hormonal suppression should be the initial mode of treatment for women with suspected pelvic congestion. *Medroxyprogesterone acetate*, 30 mg daily, has been found to be useful (118). Percutaneous transcatheter embolization can be used in women who do not respond to medical or hormonal therapy (119). Concurrently, a multidisciplinary approach incorporating psychotherapy, behavioral pain management, or both is important. A positive interaction between *medroxyprogesterone acetate* and pain management has been noted (118). Technically more invasive, transcatheter embolotherapy selectively catheterizes the ovarian and internal iliac veins, followed by contrast venography and embolization (120). Several small, uncontrolled studies with limited follow-up have reported pain reduction with transcatheter embolization of pelvic veins (121,122,123). For women who have completed their childbearing, hysterectomy with possible oophorectomy is a reasonable option.

Subacute Salpingo-oophoritis

Patients with salpingo-oophoritis usually present with symptoms and signs of acute infection. Atypical or partially treated infection may not be associated with fever or peritoneal signs. Subacute or atypical salpingo-oophoritis is often a sequela of chlamydia or mycoplasma

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infection. Abdominal tenderness, cervical motion, and bilateral adnexal tenderness are typical of pelvic infection (see Chapter 16).

Ovarian Remnant

In a reproductive-aged patient who has had a bilateral salpingo-oophorectomy, with or **Syndrome** without a hysterectomy, for severe endometriosis or PID, chronic pelvic pain may be caused by ovarian remnant syndrome. **This syndrome results from residual ovarian cortical tissue that is left *in situ* after a difficult dissection in an attempt to perform an oophorectomy. This tissue can become encased in adhesions and result in painful cysts.** Often, the patient has had multiple pelvic operations with the uterus and adnexa removed sequentially. Laparoscopic oophorectomy, combined with a difficult dissection, is a strong risk factor (124).

It is important not to confuse ovarian remnant syndrome with residual ovary syndrome, which results after a hysterectomy in which one or both ovaries are left intact. If adhesions develop and encase the ovaries, cyclical expansion of the ovaries can result

in pain and, in some cases, a tender mass.

Symptoms

The patient usually reports lateralizing pelvic pain, often cycling with ovulation or the luteal phase, described as sharp and stabbing or as constant, dull, and nonradiating, possibly with associated genitourinary or gastrointestinal symptoms (125). Symptoms tend to arise 2 to 5 years after initial oophorectomy. A tender mass in the lateral region of the pelvis is pathognomonic. The patient may also report deep dyspareunia, constipation, or flank pain (126).

Diagnosis

Ultrasonography usually confirms a mass with the characteristics of ovarian tissue. The accuracy of ultrasound can be improved by treating the patient with a 5- to 10-day course of *clomiphene citrate* (*Clomid*), 100 mg daily, to stimulate follicular development (126). In a patient who has had bilateral salpingo-oophorectomy and is not taking hormone therapy, estradiol and follicle-stimulating hormone (FSH) assays reveal a characteristic premenopausal picture (FSH 40 mIU/mL and estradiol 30 pg/mL), although on occasion the remaining ovarian tissue may not be active enough to suppress FSH levels (126,127). The patient may have a persistent estrogenized state based on the vulvar and vaginal examination and lack postmenopausal symptoms such as hot flashes, night sweats, and mood changes (126).

Management

Initial medical treatment with *danazol*, high-dose progestins, or oral contraceptives usually provides mixed results. Patients usually experience relief of pain with a GnRH agonist, although these medications are impractical for long-term therapy (126). Those who achieve relief with GnRH agonists also experience relief with subsequent surgery (128). Laparoscopic examination is usually not productive because the ovarian mass may be missed or adhesions may prevent accurate diagnosis. Laparotomy is necessary for treatment, and the corrective surgery tends to be arduous, often involving inadvertent cystotomy, enterotomy, postoperative small bowel obstructions, and hematoma formation. Surgical pathology usually reveals the presence of ovarian tissue, sometimes with endometriosis, corpus lutea or follicle cysts, and fibrous adhesions (127,128). *Clomiphene citrate* can be used 7 to 10 days before surgery to induce folliculogenesis, allowing ovarian tissue to be found more easily.

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Gastroenterologic Causes

The uterus, cervix, and adnexa share with the lower ileum, sigmoid colon, and rectum the same visceral innervation, with pain signals traveling through sympathetic nerves to spinal cord segments T10 to L1 (129). It is often difficult, therefore, to determine whether lower abdominal pain is of gynecologic or enterocoelic origin. Skillful medical history and examination are necessary to distinguish gynecologic from gastrointestinal causes of pain. In addition, inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, infectious enterocolitis, intestinal neoplasms, appendicitis, and hernia must be ruled out with appropriate history and physical examination, complete blood count, and stool cultures as well as visualization of colonic mucosa when appropriate.

Irritable bowel syndrome (IBS) is one of the more common causes of lower abdominal pain and may account for up to 60% of referrals to the gynecologist for

chronic pelvic pain (129). An estimated 35% of patients with chronic pelvic pain have a concurrent diagnosis of IBS (130). Women who have had a hysterectomy for chronic pelvic pain are twice as likely to have IBS (131). The exact causes of IBS are unknown; however, patients with IBS have pain with smaller volume of distention of the bowel than those without IBS (132). These patients also have an abnormal pain referral pattern with colonic distention. Visceral hypersensitivity or hyperalgesia has been postulated as the cause of pain, although the cause of this hyperalgesia is not known (133).

Symptoms

The predominant symptom of IBS is abdominal pain (134). Other symptoms include abdominal distention, excessive flatulence, alternating diarrhea and constipation, increased pain before a bowel movement, decreased pain after a bowel movement, and pain exacerbated by events that increase gastrointestinal motility, such as highfat diet, stress, anxiety, depression, and menses. The pain is usually intermittent, occasionally constant, cramplike, and more likely to occur in the left lower quadrant. The patient with IBS can be placed into one of three categories: constipation-predominant, diarrhea-predominant, and pain-predominant (alternating bowel habits) depending on their main symptoms (135). The Rome II criteria for diagnosis (Table 14.4) include at least 12 weeks (not necessarily consecutive) in the preceding 12 months of abdominal discomfort or pain that has at least two of the following features: relief with defecation, onset associated with change in stool frequency, or onset associated with change in form (appearance) of stool (136,137).

Signs

On physical examination, the findings of a palpable tender sigmoid colon or discomfort during insertion of the finger into the rectum and hard feces in the rectum are suggestive of IBS (129).

Diagnosis

The diagnosis of IBS is usually based on history and physical examination, and although suggestive, especially in young women, the findings are not specific. In one study, 91% of patients with IBS had two or more IBS symptoms (abdominal distention, relief of pain with bowel movement, more frequent bowel movements with the onset of pain, looser bowel movements with the onset of pain), whereas 30% of patients with organic disease had two or more of these symptoms (138). Therefore, a complete blood count, stool sample to test for white cells and occult blood, and sigmoidoscopy or colonoscopy or barium enema are usually required, particularly in older individuals and in young individuals who have not responded to initial treatment (139). The results of these studies are all normal in patients with IBS.

Management

Current medical therapy for IBS is generally unsatisfactory, and placebo response rates are high (140). Treatment consists of reassurance, education, stress reduction, bulk-forming agents and other symptomatic treatments, and low-dose tricyclic antidepressants (139,141). These patients should eliminate triggers in their diet, such as food containing lactose, sorbitol, alcohol, fat, and fructose. Products that contain caffeine can also cause abdominal bloating, cramping, and more frequent bowel movements. After the patient has tried these lifestyle changes, if she remains symptomatic, a short-term trial

of antispasmodics such as *dicyclomine* or *hyoscyamine* can be given (139,141). Finally, *Tegaserod*, which is a 5-HT₄ agonist, approved by the U.S. Food and Drug Administration for treatment of IBS, can be used on a short-term trial basis (141).

A multidisciplinary management approach consisting of medical and psychological approaches is recommended. It addresses the cognitive, affective, and behavioral components of the pain. Therapy may decrease the intensity of nociceptor stimulation as well as change the interpretation of the meaning of pain.

Urologic Causes

Chronic pelvic pain of urologic origin may be related to recurrent cystourethritis, urethral syndrome, sensory urgency of uncertain cause, as well as interstitial cystitis.

With an appropriate diagnostic workup, infiltrating bladder tumors, ureteral obstruction, renal lithiasis, and endometriosis can easily be ruled out as possible causes.

Urethral Syndrome

Urethral syndrome is defined as a symptom complex including dysuria, frequency and urgency of urination, suprapubic discomfort, and often dyspareunia in the absence of any abnormality of the urethra or bladder. The cause of urethral syndrome is uncertain and has been attributed to a subclinical infection, urethral obstruction, and psychogenic and allergic factors (142). The symptoms of urethral syndrome may actually evolve into the initial stages of interstitial cystitis.

Symptoms

Urinary urgency, frequency, suprapubic pressure, and other less frequent symptoms such as bladder or vaginal pain, urinary incontinence, postvoid fullness, dyspareunia, and suprapubic pain are commonly observed.

Signs

Physical and neurologic examinations should be performed. The anal reflex should document that S₂ to S₄ spinal segments have not been interrupted (142). Anatomic abnormalities, including pelvic relaxation, urethral caruncle, and hypoestrogenism, should be evaluated. The patient should also be evaluated for vaginitis. The urethra should be carefully palpated to detect purulent discharge.

Diagnosis

A clean catch or catheterized urine specimen for routine urinalysis and culture should be obtained to rule out urinary tract infection. As indicated, urethral and cervical cultures for chlamydia should be obtained, and a wet prep for vaginitis should be performed. Urethral syndrome should be considered if the results of urine and urethral cultures are negative, the evaluation does not disclose vulvovaginitis, and no allergic phenomenon causing contact dermatitis of the urethra can be detected. The possibility of ureoplasma, chlamydia, candida, trichomonas, gonorrhea, and herpes should be eliminated. Cystoscopic evaluation should be performed to rule out urethral diverticulum, interstitial cystitis, and cancer.

Management

Various forms of therapy have been suggested for urethral syndrome. Those patients in whom no infectious agent is present but who have sterile pyuria respond to a 2- to 3-week course of *doxycycline* or *erythromycin* (142). Long-term, low-dose antimicrobial prophylaxis is often used in women with urgency and frequency symptoms who have had a history of recurrent urinary tract infections. Some of these women may continue to have symptoms when their urine is not infected, and then bacterial infection redevelops over time (142). It is recommended that all postmenopausal women be given a trial of local estrogen therapy for about 2 months. If there is no improvement after antibiotic or estrogen therapy, urethral dilation can be considered. Positive results also have been noted with biofeedback techniques (142).

Interstitial Cystitis

Interstitial cystitis occurs more often in women than men. Most patients are between 40 and 60 years of age. The cause of interstitial cystitis is unknown, although an autoimmune etiology is generally accepted (142).

Symptoms

Symptoms include severe and disabling urinary frequency and urgency, nocturia, dysuria, and occasional hematuria. Suprapubic, pelvic, urethral, vaginal, or perineal pain is common and can be relieved to some extent by emptying of the bladder.

Signs

Pelvic examination usually reveals anterior vaginal wall and suprapubic tenderness. Urinalysis may reveal microhematuria without pyuria, although results may be normal.

Diagnosis

The diagnosis is based on symptoms and characteristic cystoscopic findings (142,143). The use of a pelvic pain and urgency/frequency symptom scale and a bladder potassium intravesical test can promote early diagnosis (144); however, it is still a point of debate as to whether a positive potassium test is definitive for interstitial cystitis or if it just shows bladder hyperalgesia. Cystoscopy performed in a conscious patient may reveal only bladder hypersensitivity; with anesthesia, however, and sufficient distention of the bladder, submucosal hemorrhages and cracking of the mucosa may be noted along with characteristic glomerulations, Hunner's ulcers or patches, and fibrosis (129,145,146). Although the histologic features of the biopsy specimen are nonspecific, there is usually submucosal edema, vasodilation, and infiltration by macrophages, plasma cells, and eosinophils.

Management

Because the etiology is uncertain, management has been empirical. Diet changes, stress reduction, and behavioral changes can be initiated, such as recording a voiding diary and training the pelvic floor muscle (146). Various pharmaceutical approaches, including anticholinergic, antispasmodic, and anti-inflammatory agents, have been used. Response to treatment also has been noted with the use of tricyclic antidepressants or *pentosan polysulfate sodium*, which is approved for therapy (145). Hydrostatic bladder distention may produce temporary relief by creating detrusor ischemia and decreased innervation of the bladder wall, and repeated bladder instillations of heparin with lidocaine are useful. Biofeedback, TENS, and behavioral therapy have also been used with some success (142).

Neurologic and Musculoskeletal Causes

Nerve Entrapment

Abdominal cutaneous nerve injury or entrapment may occur spontaneously or within weeks to years after transverse suprapubic skin or laparoscopy incisions (70,147). The ilioinguinal (T12 and L1) or iliohypogastric (T12 and L1) nerves may become trapped between the transverse and internal oblique muscles, especially when the muscles contract. Alternatively, the nerve may be ligated or traumatized during the surgery. **Femoral nerve injury, one of the most commonly injured nerves in gynecologic laparotomies, usually results when deep lateral retractor blades compress the nerve between the blade and the lateral pelvic side wall** (148,149). Symptoms of nerve entrapment include sharp, burning, aching pain and paresthesias in the dermatomal distribution of the involved nerve (4,150,151). Femoral nerve damage results in inability to flex at the hip joint or to extend at the knee (148,149). In general with nerve entrapment, hip flexion and exercise or activity exacerbates pain and rest or infiltration with a local anesthetic relieves pain (152). The pain is usually judged as coming from the abdomen, not the skin.

Signs

On examination, the pain usually can be localized with the fingertip. The maximal point of tenderness in an iliohypogastric or ilioinguinal injury is usually at the rectus margin, medial and inferior to the anterior iliac spine. A tentative diagnosis can be confirmed by diagnostic nerve block with 3 to 5 mL of 0.25% *bupivacaine*. Patients usually report immediate relief of symptoms after injection, and at least 50% experience relief lasting longer than a few hours over a week or two (70).

Management

Many patients may require no further intervention after nerve block, although some patients require up to five biweekly injections. If injection is successful in producing only limited pain relief and there are no contributory visceral or psychological factors, cryoneurolysis or surgical removal of the involved nerve is recommended. Medication for neuropathic pain such as anticonvulsants or antidepressants may be useful.

Myofascial Pain

Myofascial syndrome has been documented in about 15% of patients with chronic pelvic pain (152). These patients are noted to have **trigger points, which are hyperirritable areas within a tight band of skeletal muscle or within its fascia** (153,154). Trigger points are initiated by pathogenic autonomic reflex of visceral or muscular origin (154,155,156). They are painful on compression. The referred pain of the trigger point occurs in a dermatomal distribution, and it is thought to be caused by nerves from the muscle or deeper structures sharing a common second-order neuron in the spinal cord. The patient can experience weakness and restriction in range of motion of the affected muscle. Painful trigger points characteristically can be abolished with the injection of local anesthetic into the painful area (153). Trigger points are often present in women with chronic pelvic pain irrespective of presence or type of underlying pathology. In one study, 89% of women with chronic pelvic pain had abdominal, vaginal, or lumbosacral trigger points (153). In the absence of the initial or ongoing organic pathology, various factors are theorized to predispose to the chronicity of the myofascial syndrome, including psychological, hormonal, and biomechanical factors (154).

Fibromyalgia, a myofascial pain syndrome, is made up of the triad of diffuse pain, fatigue, and nonrestorative sleep (156). Women are more commonly affected than

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men. To diagnose the syndrome, the patient must have tender points in all four quadrants. It is thought to be caused a central nervous system sensitization that results in abnormal perception of chronic pain. Fibromyalgia is closely associated with chronic fatigue syndrome, a combination of regional myofascial problems including infections and autoimmune disorders or dysautonomias. The management includes education, environmental changes (well-balanced diet, adequate time for sleep, and an environment conducive to restful sleep), exercise and stretching, and counseling including techniques for relaxation and maximizing coping mechanisms (156). Medications used include NSAIDs, low-dose tricyclic antidepressants, selective serotonin reuptake inhibitors, and benzodiazepines to improve sleep (156).

Symptoms

Abdominal wall pain is often exacerbated during the premenstrual period or by stimuli to the dermatome of trigger points (e.g., full bladder, bowel, or any stimulation to organs that share the dermatome of the involved nerve) (4,150,151,155).

Signs

On examination, fingertip pressure on the trigger points evokes local and referred pain. Tensing of the rectus muscles by either straight leg lifting or raising the head off the table increases the pain. A specific jump sign can be elicited by palpation with fingertip or a cotton swab. An electric (tingling) sensation confirms correct needle placement (153).

Management

Massage therapy can help relieve the pain in some cases. "Myofascial release" is a special vigorous message that can be effective (154,156). Alternatively, sustained pressure to a trigger point with adequate force for a specified period can inactivate the irritable nerve (150,156). Injection of the trigger point with 3 mL of 0.25% bupivacaine provides relief that usually outlasts the duration of the anesthetic action. After four to five biweekly injections, the procedure should be abandoned if long-lasting relief is not obtained. Acupuncture can also be helpful (156). Concomitant with injection of trigger points, multidisciplinary pain management should be undertaken, especially if anxiety, depression, history of physical or sexual abuse, sexual dysfunction, or social or occupational disruption are present.

Low Back Pain Syndrome

In women who experience lower-back pain without pelvic pain, gynecologic pathology rarely is the cause of their pain. However, low-back pain may accompany gynecologic pathology. Back pain may be caused by gynecologic, vascular, neurologic, psychogenic, or spondylogenic (related to the axial skeleton and its structure) pathology.

Symptoms

Women with low-back pain syndrome often have pain occurring after trauma or physical exertion, in the morning on arising, or with fatigue. Nongynecologic low-back pain can intensify with the menstrual cycle.

Signs

Examination consists of inspection, evaluation with movement, and palpation. Various anatomic structures in the spine should be considered as sources of pain. Muscles, vertebral joints, and disks (including lumbosacral junction, paravertebral sacrospinal muscles, and sacroiliac joints) are common sources of spondylogenic pain that must be examined carefully (2,157).

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Diagnosis

Diagnostic imaging studies performed while the patient is standing, lying, and sitting with maximal flexion can be helpful. An elevated ESR suggests pain of inflammatory or neoplastic origin.

Management

Orthopedic or rheumatologic consultation should be sought before initiating management for back pain unless the source could be referred gynecologic pain.

Psychological Factors

From a psychological perspective, various factors may promote the chronicity of pain, including the meaning attached to the pain, anxiety, the ability to redirect attention, personality, mood state, past experience, and reinforcement contingencies that may amplify or attenuate pain (158). The Minnesota Multiphasic Personality Inventory (MMPI) studies of women with chronic pelvic pain reveal a high prevalence of a convergence "V" profile (elevated scores on the hypochondriasis, hysteria, and depression scales). Treatment of a known pathology or presumed cause without obvious physical findings that results in subjective improvement in pain severity and increased activity level produces a significant improvement in personality profile (159). **There is also a close relationship between depression and pain** (160). Both give rise to similar behavior, such as behavioral and social withdrawal and decreased activity, and may be mediated by the same neurotransmitters, including norepinephrine, serotonin, and endorphins. Antidepressants appear to relieve both depression and pain. **Childhood physical and sexual abuse has also been noted to be more prevalent in women with chronic pelvic pain than in those with other types of pain** (52% versus 12%) (161,162). In a comparison of women with chronic pelvic pain, women with nonpelvic chronic pain (headache), and pain-free women, a higher lifetime prevalence of major sexual abuse (56%) and physical abuse (50%) was found in the chronic pelvic pain group (163). However, another study of chronic pain syndromes and their relation to childhood abuse found that severe childhood sexual abuse did not seem to directly affect chronic pain, whereas childhood physical abuse did influence it (164). Childhood sexual abuse had a greater impact on depression, but childhood physical violence did not (164). Individual differences in personality and habitual coping strategies may also influence response to pain and pain recurrence. Childhood abuse possibly leads to an increased vulnerability to psychosocial stress and impaired coping strategies (164).

If patients are taught self-efficacy and adaptive pain coping skills through psychological treatment interventions, pain can be reduced and functioning improved. Dramatizing the pain is a coping mechanism that is used by pain sufferers to generate support from others around them (165). This practice, combined with pain-related anxiety and fear, propagates pain (159).

Management of Chronic Pelvic Pain

Multidisciplinary Approach

In patients with no obvious pathology and in those with pathology that has an equivocal role in pain production, multidisciplinary therapy is usually preferable. This approach incorporates the skills of the gynecologist, psychologist, and physical therapist.

The approach to women with chronic pain must be therapeutic, optimistic, supportive, and sympathetic. Offering regular follow-up appointments is preferable to asking the

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patient to return only if pain persists because the latter reinforces pain behavior. Specific pain management skills should be taught using cognitive/behavioral approaches. Women are offered ways to enhance opportunities for control of pain. Psychotherapy is indicated for women who have pronounced depression, sexual difficulties, or indications of past trauma. Various strategies, including relaxation techniques, stress management, sexual and marital counseling, hypnosis, and other psychotherapeutic approaches, have been found to be crucial. Psychological group treatment has also been shown to be a very cost-effective approach for helping patients to learn stress reduction techniques and develop coping behavioral mechanisms (166). Acupuncture may also be helpful (167). Uterosacral, inferior and superior hypogastric, iliohypogastric, pudendal, or epidural nerve blocks should be used where appropriate (13,14,168).

Various studies of multidisciplinary pain management have been performed. Retrospective, uncontrolled studies revealed relief of pain in 85% of the subjects (167,169). One prospective randomized study revealed a similar response rate, which was significantly better than that of traditional therapy for pain and associated symptom reduction, improvement of daily functioning, and quality of life (170).

Medical Therapy

A low dose of a tricyclic antidepressant, anticonvulsant, or selective serotonin/norepinephrine reuptake inhibitor is combined with cognitive behavioral therapy directed toward reducing reliance on pain medication, increasing activity, and relieving the impact the pain has on the women's overall lifestyle (13,14). Women with depression should be treated with an appropriate therapeutic dose of antidepressant medication. Antidepressants such as tricyclic antidepressants in low doses or serotonin/norepinephrine reuptake inhibitors (SNRIs) that elevate central norepinephrine concentrations are useful for pain modulation and pain reduction. Only one small, randomized, controlled trial has looked at the effect of selective serotonin reuptake inhibitors on pelvic pain. It failed to show a significant difference in pain or functional ability in a short follow-up period (171).

Surgical Therapy

Laparoscopy

Women with disabling cyclic pain that does not respond to nonsteroidal anti-inflammatory medication or oral contraceptives should undergo laparoscopic evaluation. Diagnostic laparoscopy has become a standard procedure in the evaluation of patients with chronic noncyclic pelvic pain; however, laparoscopy should be withheld until other nongynecologic somatic or visceral causes of pain have been excluded. During diagnostic laparoscopy, endometriotic lesions should be excised for

biopsy, and if infection is suspected, cultures should be performed. All visible endometriosis should be surgically excised or electrocoagulated. Patients with dysmenorrhea may benefit from transection of the uterosacral ligaments. The uterosacral ligaments carry the principal afferent nerve supply from the uterus to the hypogastric nerve. The original procedure was performed by colpotomy and had a success rate of 70% (172). Laparoscopic nerve ablation was found to relieve dysmenorrhea in 85% of patients (173). Nonrandomized retrospective and prospective studies have suggested that diagnostic laparoscopy provides a positive psychological effect on the treatment of chronic pelvic pain; however, this should not be the main goal of laparoscopy (174).

Lysis of Adhesions

The role of pelvic adhesions in pain is unclear, and the efficacy of lysis of adhesions is even more in doubt. Adhesiolysis, even via laparoscopy, is frequently complicated by adhesion reformation and has not been shown to be effective for relief of pain in

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controlled trials (107,175,176). Other causes must be treated first, and psychological consultation and management should precede or accompany the lysis of adhesions.

Presacral Neurectomy and Uterine Nerve Ablation

Presacral neurectomy or sympathectomy was first described for dysmenorrhea (177).

Laparoscopic uterine nerve ablation (LUNA) was developed to offer a more technically straightforward, permanent surgical procedure for chronic pelvic pain (178).

The discovery of highly successful medical therapies has largely supplanted presacral neurectomy and LUNA; however, presacral neurectomy and LUNA may be indicated for primary or secondary dysmenorrhea unrelieved by traditional therapy and unresponsive to multidisciplinary pain management. The response rate to

presacral neurectomy for secondary dysmenorrhea varies between 50% and 75% (176). LUNA and presacral neurectomy for primary dysmenorrhea have not been found to provide statistically significant differences in short-term pain relief, but it appears that presacral neurectomy may be more effective than LUNA in the long term (176). The neurectomy only relieves pain deriving from the cervix, uterus, and proximal fallopian tubes (T11 to L2). The nerve supply to the adnexal structures (T9 to T10) bypasses the hypogastric nerve.

Therefore, lateralizing visceral pain is unlikely to be relieved by presacral neurectomy.

Intraoperative complications, such as hemorrhage or ureteral injury, can occur in a small percentage of cases. The sacral nerve supply is unaffected by division of the presacral nerve; thus, normal micturition, defecation, and parturition are preserved. A local anesthetic hypogastric block performed under fluoroscopic guidance can help to predict the response to this operation.

Hysterectomy

Although 19% of hysterectomies are performed to cure pelvic pain, 30% of patients presenting to pain clinics have already undergone hysterectomy without experiencing pain relief (63,64). A multidisciplinary approach including a gynecologist, physical therapist, and a psychologist was shown to decrease the frequency of hysterectomies in one study from 16.3% of patients with chronic pelvic pain to 5.8% (179).

Hysterectomy is particularly useful for women who have completed childbearing and have secondary dysmenorrhea or chronic pain related to endometriosis, to uterine pathology, such as adenomyosis, or to pelvic congestion. Before recommending hysterectomy for pain or unilateral adnexectomy for unilateral pain, it is useful to apply the **PREPARE** mnemonic

in discussions with the patient (180): the **P**rocedure that is being done, **R**eason or indication, **E**xpectation or desired outcome of the procedure, **P**robability that the outcome will be achieved, **A**lternatives and nonsurgical options, and **R**isks as well as **E**xpense (see Chapter 3). Hysterectomy for central pelvic pain in women with dysmenorrhea, dyspareunia, and uterine tenderness provided relief of pain in 77% of women in one retrospective study (181) and in 74% of women in one prospective cohort study (182). Nevertheless, 25% of women in the retrospective study noted that pain persisted or worsened at 1-year follow-up (181). Persistent pain in the prospective study was associated with multiparity, prior history of PID, absence of pathology, and Medicaid payer status (182).

The American College of Obstetricians and Gynecologists has outlined criteria that should be met before performing a hysterectomy for pelvic pain (183). They require at least 6 months of pelvic pain without any otherwise correctable pathology. When deciding on the surgical approach, consideration should be given to a vaginal or laparoscopic hysterectomy over an abdominal approach if there are no extensive adhesions expected or large uterine/fibroid size does not preclude it. There have been many studies that confirm less morbidity and shorter hospital stays with vaginal compared with abdominal hysterectomies (184,185). A prospective study of abdominal versus vaginal versus

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laparoscopically assisted surgery did not find any statistical difference or worsening of outcomes of urinary or sexual function between the different approaches at 6 months (185).

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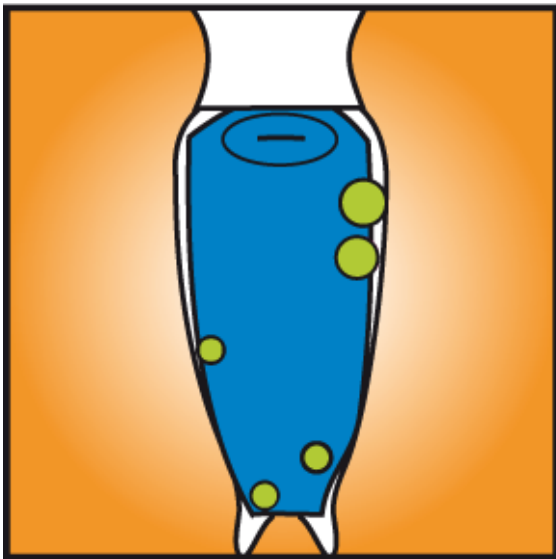
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16

Genitourinary Infections and Sexually Transmitted Diseases

David E. Soper



- **Vaginitis is diagnosed by office-based testing.**
- **More prolonged antifungal therapy is indicated for women with complicated vulvovaginal candidiasis (VVC) than for those with uncomplicated disease.**
- **Women with normal physical examination findings and no evidence of fungal infection disclosed by microscopy are unlikely to have VVC and should not be treated empirically unless results of a vaginal yeast culture are positive.**
- **Cervicitis is commonly associated with bacterial vaginosis (BV), which, if not treated concurrently, leads to significant persistence of the symptoms and signs of cervicitis.**
- **Metronidazole should be included in the antimicrobial regimen used to treat patients with pelvic inflammatory disease (PID) if concurrent bacterial vaginosis**

is present.

- **Trocar drainage, with or without placement of a drain, is successful in as many as 90% of patients with PID complicated by tubo-ovarian abscess that fails to respond to antimicrobial therapy within 72 hours.**
- **Because false-negative results are common with herpes simplex virus (HSV) cultures, especially in patients with recurrent infections, type-specific glycoprotein G-based antibody assay tests are useful in confirming a clinical diagnosis of genital herpes.**
- **Suppressive treatment partially decreases symptomatic and asymptomatic viral shedding and the potential for transmission.**

Genitourinary tract infections are among the most frequent disorders for which patients seek care from gynecologists. By understanding the pathophysiology of these diseases and having an effective approach to their diagnosis, physicians can institute appropriate antimicrobial therapy to treat these conditions and reduce long-term sequelae.

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The Normal Vagina

Normal vaginal secretions are composed of vulvar secretions from sebaceous, sweat, Bartholin, and Skene glands; transudate from the vaginal wall; exfoliated vaginal and cervical cells; cervical mucus; endometrial and oviductal fluids; and micro-organisms and their metabolic products. The type and amount of exfoliated cells, cervical mucus, and upper genital tract fluids are determined by biochemical processes that are influenced by hormone levels (1).

Vaginal secretions may increase in the middle of the menstrual cycle because of an increase in the amount of cervical mucus. These cyclic variations do not occur when oral contraceptives are used and ovulation does not occur.

The vaginal desquamative tissue is made up of vaginal epithelial cells that are responsive to varying amounts of estrogen and progesterone. Superficial cells, the main cell type in women of reproductive age, predominate when estrogen stimulation is present. Intermediate cells predominate during the luteal phase because of stimulation by progesterone. Parabasal cells predominate in the absence of either hormone, a condition that may be found in postmenopausal women who are not receiving hormonal therapy.

The normal vaginal flora is mostly aerobic, with an average of six different species of bacteria, the most common of which is hydrogen peroxide-producing lactobacilli.

The microbiology of the vagina is determined by factors that affect the ability of bacteria to survive (2). These factors include vaginal pH and the availability of glucose for bacterial metabolism. **The pH level of the normal vagina is lower than 4.5, which is maintained by the production of lactic acid.** Estrogen-stimulated vaginal epithelial cells are rich in glycogen. Vaginal epithelial cells break down glycogen to monosaccharides, which can then be converted by the cells themselves, and lactobacilli to lactic acid.

Normal vaginal secretions are floccular in consistency, white in color, and usually located in the dependent portion of the vagina (posterior fornix). Vaginal secretions can be analyzed by a wet-mount preparation. A sample of vaginal secretions is suspended in 0.5 mL of normal saline in a glass tube, transferred to a slide, covered with a slip, and assessed

by microscopy. Some clinicians prefer to prepare slides by suspending secretions in saline placed directly on the slide. Secretions should not be placed on the slide without saline because this method causes drying of the vaginal secretions and does not result in a well-suspended preparation. Microscopy of normal vaginal secretions reveals many superficial epithelial cells, few white blood cells (less than 1 per epithelial cell), and few, if any, clue cells. **Clue cells are superficial vaginal epithelial cells with adherent bacteria, usually *Gardnerella vaginalis*, which obliterates the crisp cell border when visualized microscopically.** Potassium hydroxide 10% (KOH) may be added to the slide, or a separate preparation can be made, to examine the secretions for evidence of fungal elements. The results are negative in women with normal vaginal microbiology. Gram stain reveals normal superficial epithelial cells and a predominance of gram-positive rods (lactobacilli).

Vaginal Infections

Bacterial Vaginosis

Bacterial vaginosis (BV) has previously been referred to as nonspecific vaginitis or *Gardnella* vaginitis. It is an alteration of normal vaginal bacterial flora that results in the loss of hydrogen peroxide-producing lactobacilli and an overgrowth of predominantly anaerobic bacteria (3,4). **The most common form of vaginitis in the United States is BV** (5). Anaerobic bacteria can be found in less than 1% of the flora of normal women. In women with BV, however, the concentration of anaerobes, as well as *G. vaginalis* and *Mycoplasma hominis*, is 100 to 1,000 times higher than in normal women. Lactobacilli are usually absent.

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It is not known what triggers the disturbance of normal vaginal flora. It has been postulated that repeated alkalization of the vagina, which occurs with frequent sexual intercourse or use of douches, plays a role. After normal hydrogen peroxide-producing lactobacilli disappear, it is difficult to reestablish normal vaginal flora, and recurrence of BV is common.

Numerous studies have shown an association of BV with significant adverse sequelae. Women with BV are at increased risk for pelvic inflammatory disease (PID) (6), postabortal PID (7), postoperative cuff infections after hysterectomy (8), and abnormal cervical cytology (9). Pregnant women with BV are at risk for premature rupture of the membranes (10), preterm labor and delivery (10), chorioamnionitis, and postcesarean endometritis (11). In women with BV who are undergoing surgical abortion or hysterectomy, perioperative treatment with *metronidazole* eliminates this increased risk (12,13).

Diagnosis

Office-based testing is required to diagnose BV. It is diagnosed on the basis of the following findings (14):

- **A fishy vaginal odor, which is particularly noticeable following coitus, and vaginal discharge are present.**
- **Vaginal secretions are gray and thinly coat the vaginal walls.**
-

The pH of these secretions is higher than 4.5 (usually 4.7 to 5.7).

- **Microscopy of the vaginal secretions reveals an increased number of clue cells, and leukocytes are conspicuously absent. In advanced cases of BV, more than 20% of the epithelial cells are clue cells.**
- **The addition of KOH to the vaginal secretions (the "whiff" test) releases a fishy, aminelike odor.**

Clinicians unable to perform microscopy should use alternative diagnostic tests such as a pH and amines test card, detection of *G. vaginalis* ribosomal RNA, or Gram stain (15). Culture of *G. vaginalis* is not recommended as a diagnostic tool because of its lack of specificity.

Treatment

Ideally, treatment of BV should inhibit anaerobes but not vaginal lactobacilli. **The following treatments are effective (16):**

- ***Metronidazole*, an antibiotic with excellent activity against anaerobes but poor activity against lactobacilli, is the drug of choice for the treatment of BV.** A dose of 500 mg administered orally twice a day for 7 days should be used. Patients should be advised to avoid using alcohol during treatment with oral *metronidazole* and for 24 hours thereafter.
- ***Metronidazole* gel, 0.75%, one applicator (5 g) intravaginally once or twice daily for 5 days, may also be prescribed.**

The overall cure rates range from 75% to 84% with the aforementioned regimens (16). ***Clindamycin* in the following regimens also is effective in treating BV:**

- ***Clindamycin* cream, 2%, one applicator full (5 g) intravaginally at bedtime for 7 days**
- ***Clindamycin*, 300 mg, orally twice daily for 7 days**

- ***Clindamycin* ovules, 100 mg, intravaginally once at bedtime for 3 days**
- ***Clindamycin* bioadhesive cream, 2%, 100 mg intravaginally in a single dose**

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Many clinicians prefer intravaginal treatment to avoid systemic side effects such as mild to moderate gastrointestinal upset and unpleasant taste. Treatment of the male sexual partner has not been shown to improve therapeutic response and therefore is not recommended.

Trichomonas Vaginitis

Trichomonas vaginitis is caused by the sexually transmitted, flagellated parasite, *Trichomonas vaginalis*. The transmission rate is high; 70% of men contract the disease after a single exposure to an infected woman, which suggests that the rate of male-to-female transmission is even higher. The parasite, which exists only in trophozoite form, is an anaerobe that has the ability to generate hydrogen to combine with oxygen to create an anaerobic environment. It often accompanies BV, which can be diagnosed in as many as 60% of patients with trichomonas vaginitis.

Diagnosis

Local immune factors and inoculum size influence the appearance of symptoms. Symptoms and signs may be much milder in patients with a small inocula of trichomonads, and trichomonas vaginitis often is asymptomatic (17,18).

- **Trichomonas vaginitis is associated with a profuse, purulent, malodorous vaginal discharge that may be accompanied by vulvar pruritus.**
- **Vaginal secretions may exude from the vagina.**
- **In patients with high concentrations of organisms, a patchy vaginal erythema and colpitis macularis ("strawberry" cervix) may be observed.**
- **The pH of the vaginal secretions is usually higher than 5.0.**
- **Microscopy of the secretions reveals motile trichomonads and increased numbers of leukocytes.**
- **Clue cells may be present because of the common association with BV.**
- **The whiff test may be positive.**

Morbidity associated with trichomonal vaginitis may be related to BV. Patients with trichomonas vaginitis are at increased risk for postoperative cuff cellulitis following hysterectomy (8). **Pregnant women with trichomonas vaginitis are at increased risk for premature rupture of the membranes and preterm delivery.** Because of the sexually transmitted nature of trichomonas vaginitis, women with this infection should be tested for other sexually transmitted diseases (STDs), particularly *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Serologic testing for syphilis and human immunodeficiency virus (HIV) infection should also be considered.

Treatment

The treatment of trichomonal vaginitis can be summarized as follows:

- **Metronidazole is the drug of choice for treatment of vaginal trichomoniasis.** Both a single-dose (2 g orally) and a multidose (500 mg twice daily for 7 days) regimen are highly

effective and have cure rates of about 95%.

- **The sexual partner should also be treated.**
- ***Metronidazole* gel, although highly effective for the treatment of BV, should not be used for the treatment of vaginal trichomoniasis.**
- **Women who do not respond to initial therapy should be treated again with *metronidazole*, 500 mg, twice daily for 7 days.** If repeated treatment is not effective, the patient should be treated with a single 2-g dose of *metronidazole* once daily for 5 days or *tinidazole*, 2 g, in a single dose for 5 days.
- **Patients who do not respond to repeated treatment with *metronidazole* or *tinidazole* and for whom the possibility of reinfection has been excluded should be referred for expert consultation.** In these uncommon refractory cases, an important part of management is to obtain cultures of the parasite to determine its susceptibility to *metronidazole* and *tinidazole*.

Vulvovaginal Candidiasis

An estimated 75% of women experience at least one episode of vulvovaginal candidiasis (VVC) during their lifetimes (19). Nearly 45% of women will experience two or more episodes (20). Fortunately, few are plagued with a chronic, recurrent infection.

Candida albicans is responsible for 85% to 90% of vaginal yeast infections. Other species of *Candida*, such as *C. glabrata* and *C. tropicalis*, can cause vulvovaginal symptoms and tend to be resistant to therapy. *Candida* are dimorphic fungi existing as blastospores, which are responsible for transmission and asymptomatic colonization, and as mycelia, which result from blastospore germination and enhance colonization and facilitate tissue invasion. The extensive areas of pruritus and inflammation often associated with minimal invasion of the lower genital tract epithelial cells suggest that an extracellular toxin or enzyme may play a role in the pathogenesis of this disease. A hypersensitivity phenomenon also may be responsible for the irritative symptoms associated with VVC, especially for patients with chronic, recurrent disease. Patients with symptomatic disease usually have an increased concentration of these micro-organisms ($>10^4/\text{mL}$) compared with asymptomatic patients ($<10^3/\text{mL}$) (21).

Factors that predispose women to the development of symptomatic VVC include antibiotic use (22,23), pregnancy (24), and diabetes (25). Pregnancy and diabetes are both associated with a qualitative decrease in cell-mediated immunity, leading to a higher incidence of candidiasis.

It is helpful to categorize women with VVC as having either uncomplicated or complicated disease (Table 16.1).

Table 16.1 Classification of Vulvovaginal Candidiasis

<i>Uncomplicated</i>	<i>Complicated</i>
Sporadic or infrequent in occurrence	Recurrent symptoms
Mild to moderate symptoms	Severe symptoms
Likely to be <i>Candida albicans</i>	Non- <i>albicans</i> <i>Candida</i>
Immunocompetent women	Immunocompromised, e.g., diabetic women

From **Sobel JD, Faro S, Force RW, et al.** Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol* 1998; 178:203–211.

Diagnosis

The symptoms of VVC consist of vulvar pruritus associated with a vaginal discharge that typically resembles cottage cheese.

- **The discharge can vary from watery to homogeneously thick.** Vaginal soreness, dyspareunia, vulvar burning, and irritation may be present. External dysuria ("splash" dysuria) may occur when micturition leads to exposure of the inflamed vulvar and vestibular epithelium to urine. Examination reveals erythema and edema of the labia and vulvar skin. Discrete pustulopapular peripheral lesions may be present. The vagina may be erythematous with an adherent, whitish discharge. The cervix appears normal.
- **The pH of the vagina in patients with VVC is usually normal (<4.5).**
- **Fungal elements, either budding yeast forms or mycelia, appear in as many as 80% of cases.** The results of saline preparation of the vaginal secretions usually are normal, although there may be a slight increase in the number of inflammatory cells in severe cases.
- **The whiff test is negative.**
- **A presumptive diagnosis can be made in the absence of fungal elements confirmed by microscopy if the pH and the results of the saline preparation evaluations are normal and the patient has increased erythema based on examination of the vagina or vulva. A fungal culture is recommended to confirm the diagnosis. Conversely, women with a normal physical examination findings and no evidence of fungal elements disclosed by microscopy are unlikely to have VVC and should not be empirically treated unless a vaginal yeast culture is positive.**

Treatment

-

Topically applied azole drugs are the most commonly available treatment for VVC and are more effective than *nystatin* (16) (Table 16.2). Treatment with azoles results in relief of symptoms and negative cultures in 80% to 90% of patients who have completed therapy. Symptoms usually resolve in 2 to 3 days. There is a trend to shorten the duration of therapy to 1 to 3 days. Although the shorter period of therapy implies a shortened duration of treatment, the short-course formulations have higher concentrations of the antifungal agent, causing an inhibitory concentration in the vagina that persists for several days.

• **An oral antifungal agent, *fluconazole*, used in a single 150-mg dose, has been approved for the treatment of VVC.** It appears to have equal efficacy when compared with topical azoles in the treatment of mild to moderate VVC (26). Patients should be advised that their symptoms will persist for 2 to 3 days so they will not expect additional treatment.

• **Women with complicated VVC benefit from an additional 150-mg dose of *fluconazole* given 72 hours after the first dose. Patients with complications also can be treated with a more prolonged topical regimen lasting 10 to 14 days. Adjunctive treatment with a weak topical steroid, such as 1% *hydrocortisone* cream, may be helpful in relieving some of the external irritative symptoms.**

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Table 16.2 Vulvovaginal Candidiasis—Topical Treatment Regimens

<i>Butoconazole</i>
2% cream, 5 g intravaginally for 3 days ^{a,b}
2% cream, 5 g BI-BSR, single intravaginal application ^a
<i>Clotrimazole</i>
1% cream, 5 g intravaginally for 7–14 days ^{a,b}
100-mg vaginal tablet for 7 days ^{a,b}
100-mg vaginal tablet, two tablets for 3 days ^a
500-mg vaginal tablet, single dose ^a
<i>Miconazole</i>
2% cream, 5 g intravaginally for 7 days ^{a,b}
200-mg vaginal suppository for 3 days ^a
100-mg vaginal suppository for 7 days ^{a,b}
<i>Nystatin</i>
100,000-Units vaginal tablet, one tablet for 14 days
<i>Ticonazole</i>
6.5% ointment, 5 g intravaginally, single dose ^a
<i>Terconazole</i>
0.4% cream, 5 g intravaginally for 7 days ^a
0.8% cream, 5 g intravaginally for 3 days ^a
80-mg suppository for 3 days ^a

^aOil-based, may weaken latex condoms.

^bAvailable as over-the-counter preparation. Adapted from **Centers for Disease Control and Prevention**. *The sexually transmitted diseases treatment guidelines*. Centers for Disease Control and Prevention. 2002; MMWR 2002; 51: RR-6. with permission.

Recurrent Vulvovaginal Candidiasis

A small number of women develop recurrent VVC (RVVC), defined as four or more episodes in a year. These women experience persistent irritative symptoms of the vestibule and vulva. Burning replaces itching as the prominent symptom in patients with RVVC. The diagnosis should be confirmed by direct microscopy of the vaginal secretions and by fungal culture. **Many women with RVVC presume incorrectly they have a chronic yeast infection. Many of these patients have chronic atopic dermatitis or atrophic vulvovaginitis.**

The treatment of patients with RVVC consists of inducing a remission of chronic symptoms with *fluconazole* (150 mg every 3 days for 3 doses). Patients should then be maintained on a suppressive dose of this agent (*fluconazole*, 150 mg weekly) for 6 months. On this regimen, 90% of women with RVVC will remain in remission. After suppressive therapy, approximately one half will remain asymptomatic. Recurrence will occur in the other half and should prompt reinstitution of suppressive therapy (27).

Inflammatory Vaginitis

***Desquamative inflammatory vaginitis* is a clinical syndrome characterized by diffuse exudative vaginitis, epithelial cell exfoliation, and a profuse purulent vaginal discharge** (28). The cause of inflammatory vaginitis is unknown, but Gram stain findings reveal a relative absence of normal long gram-positive bacilli (lactobacilli) and

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their replacement with gram-positive cocci, usually streptococci. Women with this disorder have a purulent vaginal discharge, vulvovaginal burning or irritation, and dyspareunia. A less frequent symptom is vulvar pruritus. Vaginal erythema is present, and there may be an associated vulvar erythema, vulvovaginal ecchymotic spots, and colpitis macularis. The pH of the vaginal secretions is uniformly higher than 4.5 in these patients.

Initial therapy is the use of 2% *clindamycin* cream, one applicator full (5 g) intravaginally once daily for 7 days. Relapse occurs in about 30% of patients, who should be retreated with intravaginal 2% *clindamycin* cream for 2 weeks. When relapse occurs in postmenopausal patients, supplementary hormonal therapy should be considered.

Atrophic Vaginitis

Estrogen plays an important role in the maintenance of normal vaginal ecology.

Women undergoing menopause, either naturally or secondary to surgical removal of the ovaries, may develop inflammatory vaginitis, which may be accompanied by an increased, purulent vaginal discharge. In addition, they may have dyspareunia and postcoital bleeding resulting from atrophy of the vaginal and vulvar epithelium. Examination reveals atrophy of the external genitalia, along with a loss of the vaginal rugae. The vaginal mucosa may be somewhat friable in areas. Microscopy of the vaginal secretions shows a predominance of parabasal epithelial cells and an increased number of leukocytes.

Atrophic vaginitis is treated with topical estrogen vaginal cream. Use of 1 g of conjugated estrogen cream intravaginally each day for 1 to 2 weeks generally provides relief. Systemic estrogen therapy should be considered to prevent recurrence of this disorder.

Cervicitis

The cervix is made up of two different types of epithelial cells: squamous epithelium and glandular epithelium. The cause of cervical inflammation depends on the epithelium affected. The ectocervical epithelium can become inflamed by the same micro-organisms that are responsible for vaginitis. In fact, the ectocervical squamous epithelium is an extension of and is continuous with the vaginal epithelium. *Trichomonas*, candida, and HSV can cause inflammation of the ectocervix. Conversely, *N. gonorrhoeae* and *C. trachomatis* infect only the glandular epithelium (29).

Diagnosis

The diagnosis of cervicitis is based on the finding of a purulent endocervical discharge, generally yellow or green in color and referred to as "mucopus" (30).

- **After removal of ectocervical secretions with a large swab, a small cotton swab is placed into the endocervical canal and the cervical mucus is extracted. The cotton swab is inspected against a white or black background to detect the green or yellow color of the mucopus.** In addition, the zone of ectopy (glandular epithelium) is friable or easily induced to bleed. This characteristic can be assessed by touching the ectropion with a cotton swab or spatula.
 - **Placement of the mucopus on a slide that can be Gram stained will reveal the presence of an increased number of neutrophils (30 per high-power field).** The presence of intracellular gram-negative diplococci, leading to the presumptive diagnosis of gonococcal endocervicitis, also may be detected. If the Gram stain results are negative for gonococci, the presumptive diagnosis is chlamydial cervicitis.
-
- **Tests for both gonorrhea and chlamydia, preferably using nuclei acid amplification tests, should be performed.** The microbial etiology of endocervicitis is unknown in about 50% of cases in which neither gonococci nor chlamydia is detected.

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Table 16.3 Treatment Regimens for Gonococcal and Chlamydial Infections

Neisseria gonorrhoeae endocervicitis

Cefixime, 400 mg orally (single dose), or

Ceftriaxone, 125 mg intramuscularly (single dose), or

Ciprofloxacin, 500 mg orally (single dose)^a, or

Ofloxacin, 400 mg orally (single dose)^a, or

Levofloxacin 250 mg orally (single dose)^a

Chlamydia trachomatis endocervicitis

Azithromycin, 1 g orally (single dose), or

Doxycycline, 100 mg orally twice daily for 7 days, or

Ofloxacin, 300 mg orally twice daily for 7 days, or

Levofloxacin, 500 mg orally for 7 days

^aQuinolones should not be used for infections acquired in California or Hawaii or through foreign travel). Adapted from **Centers for Disease Control and Prevention. The sexually transmitted diseases treatment guidelines.** Centers for Disease Control and Prevention, 2002; MMWR 2002; 51: RR-6. with permission.

Treatment of cervicitis consists of an antibiotic regimen recommended for the treatment of uncomplicated lower genital tract infection with both chlamydia and gonorrhea (16) (Table 16.3). It is imperative that all sexual partners be treated with a similar antibiotic regimen. Cervicitis is commonly associated with BV, which, if not treated concurrently, leads to significant persistence of the symptoms and signs of cervicitis.

Pelvic Inflammatory

PID is caused by micro-organisms colonizing the endocervix ascending to the Disease endometrium and fallopian tubes. It is a clinical diagnosis implying that the patient has upper genital tract infection and inflammation. The inflammation may be present at any point along a continuum that includes endometritis, salpingitis, and peritonitis (Fig. 16.1).

Pelvic inflammatory disease commonly is caused by the sexually transmitted micro-organisms *N. gonorrhoeae* and *C. trachomatis* (31,32,33). Endogenous micro-organisms found in the vagina, particularly the BV micro-organisms, also often are isolated from the upper genital tract of women with PID. The BV micro-organisms include anaerobic bacteria such as *Prevotella* and peptostreptococci as well as *G. vaginalis*. BV often occurs in women with PID, and the resultant complex alteration of vaginal flora may facilitate the ascending spread of pathogenic bacteria by enzymatically altering the cervical mucus barrier (34). Less frequently, respiratory pathogens such as *Haemophilus influenzae*, group A streptococci, and pneumococci can colonize the lower genital tract and cause PID.

Diagnosis

Traditionally, the diagnosis of PID has been based on a triad of symptoms and signs, including pelvic pain, cervical motion and adnexal tenderness, and the presence of fever. It is now recognized that there is wide variation in many symptoms and signs among women with this condition, which makes the diagnosis of acute PID difficult. Many women with PID exhibit subtle or mild symptoms that are not readily recognized as PID. Consequently, delay in diagnosis and therapy probably contributes to the inflammatory sequelae in the upper reproductive tract (35).

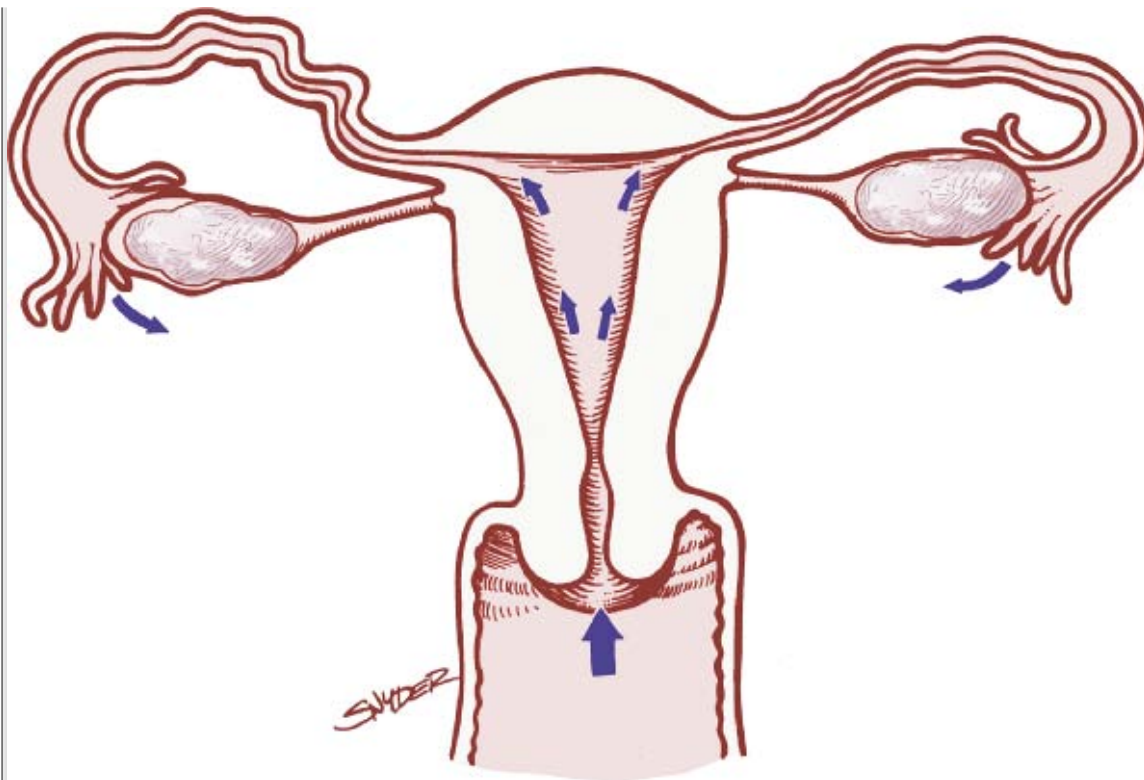


Figure 16.1 Micro-organisms originating in the endocervix ascend into the endometrium, fallopian tubes, and peritoneum, causing pelvic inflammatory disease (endometritis, salpingitis, peritonitis). (From Soper DE. Upper genital tract infections. In: Copeland LJ, ed. *Textbook of gynecology*. Philadelphia, PA: WB Saunders, 1993:521.)

In the diagnosis of PID, the goal is to establish guidelines that are sufficiently sensitive to avoid missing mild cases but sufficiently specific to avoid giving antibiotic therapy to women who are not infected. Genitourinary tract symptoms may indicate PID; therefore, the diagnosis of PID should be considered in women with any genitourinary symptoms, including, but not limited to, lower abdominal pain, excessive vaginal discharge, menorrhagia, metrorrhagia, fever, chills, and urinary symptoms (36). **Some women may develop PID without having any symptoms.**

Pelvic organ tenderness, either uterine tenderness alone or uterine tenderness with adnexal tenderness, is present in patients with PID. Cervical motion tenderness suggests the presence of peritoneal inflammation, which causes pain when the peritoneum is stretched by moving the cervix and causing traction of the adnexa on the pelvic peritoneum. Direct or rebound abdominal tenderness may be present.

Evaluation of both vaginal and endocervical secretions is a crucial part of the workup of a patient with PID (37). In women with PID, an increased number of polymorphonuclear leukocytes may be detected in a wet mount of the vaginal secretions or in the mucopurulent discharge.

More elaborate tests may be used in women with severe symptoms because an incorrect diagnosis may cause unnecessary morbidity (38) (Table 16.4). These tests include endometrial biopsy to confirm the presence of endometritis, ultrasound or radiologic tests to characterize a tubo-ovarian abscess, and laparoscopy to confirm salpingitis visually.

Table 16.4 Clinical Criteria for the Diagnosis of Pelvic Inflammatory Disease

<i>Symptoms</i>
None necessary
<i>Signs</i>
Pelvic organ tenderness
Leukorrhea and/or mucopurulent endocervicitis
<i>Additional criteria to increase the specificity of the diagnosis</i>
Endometrial biopsy showing endometritis
Elevated C-reactive protein or erythrocyte sedimentation rate
Temperature higher than 38°C
Leukocytosis
Positive test for gonorrhea or chlamydia
<i>Elaborate criteria</i>
Ultrasound documenting tubo-ovarian abscess
Laparoscopy visually confirming salpingitis

Treatment

Therapy regimens for PID must provide empirical, broad-spectrum coverage of likely pathogens (16,39), including *N. gonorrhoeae*, *C. trachomatis*, gram-negative facultative bacteria, anaerobes, and streptococci. Recommended regimens for the treatment of PID are listed in Table 16.5. **An outpatient regimen of cefoxitin and doxycycline is as effective as an inpatient parenteral regimen of the same antimicrobials (40). Therefore, hospitalization is recommended only when the diagnosis is uncertain, pelvic abscess is suspected, clinical disease is severe, or compliance with an outpatient regimen is in question. Hospitalized patients can be considered for discharge when their fever has lysed (99.5°F for more than 24 hours), the white blood cell count has become normal, rebound tenderness is absent, and repeat examination shows marked amelioration of pelvic organ tenderness (41).**

Sexual partners of women with PID should be evaluated and treated for urethral infection with chlamydia or gonorrhea (Table 16.3). One of these STDs usually is found in the male sexual partners of women with PID not associated with chlamydia or gonorrhea (42,43).

Tubo-ovarian Abscess

An end-stage process of acute PID, tubo-ovarian abscess is diagnosed when a patient with PID has a pelvic mass that is palpable during bimanual examination. The condition usually reflects an agglutination of pelvic organs (tube, ovary, bowel) forming a palpable complex. Occasionally, an ovarian abscess can result from the entrance of micro-organisms through an ovulatory site. **Tubo-ovarian abscess is treated with an antibiotic regimen administered in a hospital (Table 16.5). About 75% of women with tubo-ovarian abscess respond to antimicrobial therapy alone. Failure of medical therapy suggests the need for drainage of the abscess (44).** Although drainage may require surgical exploration, percutaneous drainage guided by imaging studies (ultrasound or computed tomography) should be used as an initial option if possible. Trocar drainage, with or without placement of a drain, is successful in up to 90% of cases in which the patient failed to respond to antimicrobial therapy after 72 hours (45).

Outpatient Treatment*Regimen A**Cefoxitin*, 2 g intramuscularly, plus *probenecid*, 1 g orally concurrently, *or**Ceftriaxone*, 250 mg intramuscularly, *or*

Equivalent cephalosporin

*Plus:**Doxycycline*, 100 mg orally 2 times daily for 14 days*With or without:**Metronidazole*, 500 mg orally 2 times daily for 14 days^a*Regimen B**Ofloxacin*, 400 mg orally 2 times daily for 14 days, *or**Levofloxacin*, 500 mg orally once daily for 14 days*With or without:**Metronidazole*, 500 mg orally 2 times daily for 14 days^a**Inpatient Treatment***Regimen A**Cefoxitin*, 2 g intravenously every 6 hours, *or*

Cefotetan, 2 g intravenously every 12 hours,

*Plus:**Doxycycline*, 100 mg orally or intravenously every 12 hours*Regimen B**Clindamycin*, 900 mg intravenously every 8 hours*Plus:**Gentamicin*, loading dose intravenously or intramuscularly (2 mg/kg of body weight) followed by a maintenance dose (1.5 mg/kg) every 8 hours^aUse of *metronidazole* recommended in those cases in which bacterial vaginosis is diagnosed concurrently with PID.Adapted from **Centers for Disease Control and Prevention**. *The sexually transmitted diseases treatment guidelines*. Centers for Disease Control and Prevention, 2002; MMWR 2002; 51: RR-6. with permission.

Other Major Infections

Genital Ulcer Disease

In the United States, most patients with genital ulcers have genital HSV or syphilis (46,47,48,49). **Chancroid is the next most common cause of sexually transmitted genital ulcers, followed by the rare occurrence of lymphogranuloma venereum (LGV) and granuloma inguinale (donovanosis). These diseases are associated with an increased risk for HIV infection.** Other infrequent and noninfectious causes of genital ulcers include abrasions, fixed drug eruptions, carcinoma, and Behçet's disease.

Diagnosis

A diagnosis based on history and physical examination alone often is inaccurate. Therefore, **all women with genital ulcers should undergo a serologic test for syphilis (49).**

Because of the consequences of inappropriate therapy, such as tertiary disease and congenital syphilis in pregnant women, diagnostic efforts are directed at excluding syphilis. Optimally, the evaluation of a patient with a genital ulcer should include dark-field examination or direct immunofluorescence testing for *Treponema pallidum*, culture or antigen testing for HSV, and culture for *Haemophilus ducreyi*. Dark-field or fluorescent microscopes and selective media to culture for *H. ducreyi* often are not available in most offices and clinics. Even after complete testing, the diagnosis remains unconfirmed in one fourth of patients with genital ulcers. For this reason, most clinicians base their initial diagnosis and treatment recommendations on their clinical impression of the appearance of the genital ulcer (Fig. 16.2) and knowledge of the most likely cause in their patient population (47).

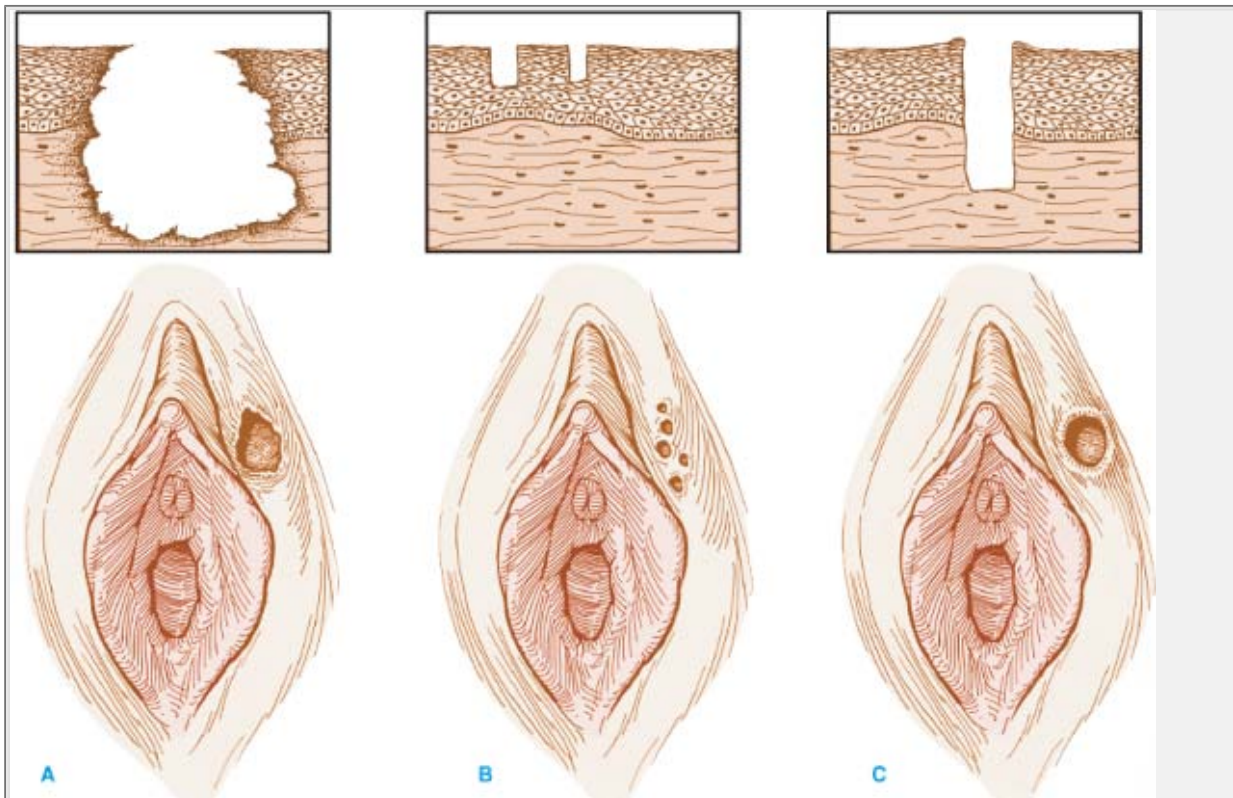


Figure 16.2 Showing the appearance of the ulcers of chancroid (A), herpes (B), and syphilis (C). The ulcer of chancroid has irregular margins and is deep with undermined edges. The syphilis ulcer has a smooth, indurated border and a smooth base. The genital herpes ulcer is superficial and inflamed. (Modified from Schmid GP, Shcalla WO, DeWitt WE. Chancroid. In: Morse SA, Moreland AA, Thompson SE, eds. *Atlas of sexually transmitted diseases*. Philadelphia, PA: JB Lippincott, 1990.)

Several clinical presentations are highly suggestive of specific diagnoses:

- **A painless and minimally tender ulcer, not accompanied by inguinal lymphadenopathy, is likely to be syphilis, especially if the ulcer is indurated.** A nontreponemal rapid plasma reagin (RPR) test, or venereal disease research laboratory (VDRL) test, and a confirmatory treponemal test—fluorescent treponemal antibody absorption (FTA ABS) or microhemagglutinin—*T. pallidum*

(MHA TP), should be used to diagnose syphilis presumptively. More recently, some laboratories screen samples with treponemal EIA tests, the results of which should be

confirmed with nontreponemal tests. The results of nontreponemal tests usually correlate with disease activity and should be reported quantitatively.

- **Grouped vesicles mixed with small ulcers, particularly with a history of such lesions, are almost always pathognomonic of genital herpes.** Nevertheless, laboratory confirmation of the findings is recommended because the diagnosis of genital herpes is traumatic for many women, alters their self-image, and affects their perceived ability to enter new sexual relationships and bear children. Culture is the most sensitive and specific test; sensitivity approaches 100% in the vesicle stage and 89% in the pustular stage and drops to as low as 33% in patients with ulcers. Nonculture tests are about 80% as sensitive as culture tests. Because false-negative results are common with HSV cultures, especially in patients with recurrent infections, type-specific glycoprotein G-based antibody assays are useful in confirming a clinical diagnosis of genital herpes.

- **One to three extremely painful ulcers, accompanied by tender inguinal lymphadenopathy, are unlikely to be anything except chancroid.** This is especially true if the adenopathy is fluctuant.

- **An inguinal bubo accompanied by one or several ulcers is most likely chancroid. If no ulcer is present, the most likely diagnosis is LGV.**

Treatment

Chancroid Recommended regimens for the treatment of chancroid include *azithromycin*, 1 g orally in a single dose; *ceftriaxone*, 250 mg intramuscularly in a single dose; *ciprofloxacin*, 500 mg orally twice a day for 3 days; or *erythromycin* base, 500 mg orally 4 times daily for 7 days. Patients should be reexamined 3 to 7 days after initiation of therapy to ensure the gradual resolution of the genital ulcer, which can be expected to heal within 2 weeks unless it is unusually large.

Herpes A first episode of genital herpes should be treated with *acyclovir*, 400 mg orally three times a day; or *famciclovir*, 250 mg orally three times a day; or *valacyclovir*, 1.0 g orally twice a day for 7 to 10 days or until clinical resolution is attained. Although these agents provide partial control of the symptoms and signs of clinical herpes, it neither eradicates latent virus nor affects subsequent risk, frequency, or severity of recurrences after the drug is discontinued. Daily suppressive therapy (*acyclovir*, 400 mg orally twice daily; or *famciclovir*, 250 mg twice daily; or *valacyclovir*, 1.0 g orally once a day) reduces the frequency of HSV recurrences by at least 75% among patients with six or more recurrences of HSV per year. Suppressive treatment partially, but not totally, decreases symptomatic and asymptomatic viral shedding and the potential for transmission (48).

Syphilis Parenteral administration of *penicillin G* is the preferred treatment of all stages of syphilis. *Benzathine penicillin G*, 2.4 million units intramuscularly in a single dose, is the recommended treatment for adults with primary, secondary, or early latent syphilis. The Jarisch-Herxheimer reaction—an acute febrile response accompanied by headache, myalgia, and other symptoms—may occur within the first 24 hours after any therapy for syphilis; patients should be advised of this possible adverse reaction.

Latent syphilis is defined as those periods after infection with *T. pallidum* when patients are seroreactive but show no other evidence of disease. Patients with latent syphilis of longer than 1 year's duration or of unknown duration should be treated with

benzathine penicillin G, 7.2 million units total, administered as three doses of 2.4 million units

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intramuscularly each, at 1-week intervals. All patients with latent syphilis should be evaluated clinically for evidence of tertiary disease (e.g., aortitis, neurosyphilis, gumma, and iritis). Quantitative nontreponemal serologic tests should be repeated at 6 months and again at 12 months. An initially high titer (1:32) should decline at least fourfold (two dilutions) within 12 to 24 months.

Genital Warts

External genital warts are a manifestation of human papillomavirus (HPV) infection (50). The nononcogenic HPV types 6 and 11 are usually responsible for external genital warts. The warts tend to occur in areas most directly affected by coitus, namely the posterior fourchette and lateral areas on the vulva. Less frequently, warts can be found throughout the vulva, in the vagina, and on the cervix. Minor trauma associated with coitus can cause breaks in the vulvar skin, allowing direct contact between the viral particles from an infected man and the basal layer of the epidermis of his susceptible sexual partner. Infection may be latent or may cause viral particles to replicate and produce a wart. External genital warts are highly contagious; more than 75% of sexual partners develop this manifestation of HPV infection when exposed.

The goal of treatment is removal of the warts; it is not possible to eradicate the viral infection. Treatment is most successful in patients with small warts that have been present for less than 1 year. It has not been determined whether treatment of genital warts reduces transmission of HPV. Selection of a specific treatment regimen depends on the anatomic site, size, and number of warts, as well as expense, efficacy, convenience, and potential adverse effects (Table 16.6). Recurrences more often result from reactivation of subclinical infection than reinfection by a sex partner; therefore, examination of sex partners is not absolutely necessary. However, many of these sex partners may have external genital warts and may benefit from therapy and counseling concerning transmission of warts.

Human Immunodeficiency Virus

It is estimated that almost 40% to 50% of individuals with HIV are women. Intravenous drug use and heterosexual transmission are responsible for most of the cases of acquired immunodeficiency syndrome (AIDS) in women in the United States (51). Infection with HIV produces a spectrum of disease that progresses from an asymptomatic state to full-blown AIDS. The pace of disease progression in untreated adults is variable. The median time between infection with HIV and the development of AIDS is 10 years, with a range from a few months to more than 12 years. In a study of adults infected with HIV, symptoms developed in 70% to 85% of infected adults, and AIDS

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developed in 55% to 60% within 12 years after infection. The natural history of the disease can be significantly altered by antiretroviral therapy. Women with HIV-induced altered immune function are at increased risk for infections such as tuberculosis (TB), bacterial pneumonia, and *Pneumocystis carinii* pneumonia (PCP). Because of its impact on the immune system, HIV affects the diagnosis, evaluation, treatment, and follow-up of many other diseases and may decrease the efficacy of antimicrobial therapy for some STDs.

Table 16.6 Treatment Options for External Genital and Perianal Warts

<i>Modality</i>	<i>Efficacy (%)</i>	<i>Recurrence Risk</i>
Cryotherapy	63–88	21–39
<i>Imiquimod 5% cream^a</i>	33–72	13–19
<i>Podophyllin 10%–25%</i>	32–79	27–65
<i>Podofilox 0.5%^a</i>	45–88	33–60
<i>Trichloroacetic acid 80%–90%</i>	81	36
Electrodesiccation or cautery	94	22
Laser ^b	43–93	29–95
<i>Interferon</i>	44–61	0–67

^aMay be self-applied by patients at home.

^bExpensive; reserve for patients who have not responded to other regimens.

Diagnosis

Infection is most often diagnosed by HIV type 1 antibody tests. Antibody testing begins with a sensitive screening test such as ELISA or a rapid assay. If confirmed by Western blot or other supplemental testing, a positive antibody test result confirms that a person is infected with HIV and is capable of transmitting the virus to others. HIV antibody is detectable in more than 95% of patients within 6 months of infection. Women diagnosed with any STD, particularly genital ulcer disease, should be offered HIV testing (47). **Women at risk for STD, such as those with multiple sexual partners or whose partners have multiple sexual partners, should be offered HIV testing.**

The initial evaluation of an HIV-positive woman includes screening for diseases associated with HIV such as TB and STDs, administration of recommended vaccinations (hepatitis B, pneumococcal, and influenza), and behavioral and psychosocial counseling. Intraepithelial neoplasia is strongly associated with HPV infection and has been found to occur in high frequency in women with both HPV and HIV.

Treatment

Decisions regarding the initiation of antiretroviral therapy should be guided by monitoring the laboratory parameters of HIV RNA (viral load) and CD4 T-cell count, as well as the clinical condition of the patient. The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. In general, women with acute retroviral syndrome, those within 6 months of HIV seroconversion, and patients who have symptoms should be offered treatment (52). In addition, **treatment should be offered to those women with fewer than 350 CD4 T cells or plasma HIV RNA levels exceeding 100,000 copies/mL (bDNA assay).** Patients must be willing to accept therapy to avoid the emergence of resistance caused by poor compliance. It has been shown that dual nucleoside regimens used in addition to a protease inhibitor or nonnucleoside reverse transcriptase inhibitor provide a better durable clinical benefit than monotherapy.

In addition, **patients with less than 200 CD4 T cells/ L should receive prophylaxis against opportunistic infections,** such as *trimethoprim-sulfamethoxazole* or *aerosol pentamidine* for the prevention of PCP pneumonia (52).

Urinary Tract Infection

Acute Cystitis

Women with acute cystitis generally have an abrupt onset of multiple, severe urinary tract symptoms including dysuria, frequency, and urgency associated with suprapubic or lowback pain. Suprapubic tenderness may be noted on physical examination. Urinalysis reveals pyuria and sometimes hematuria. Several factors increase the risk for cystitis, including sexual intercourse, the use of a diaphragm and a spermicide, delayed postcoital micturition, and a history of a recent urinary tract infection (53,54,55).

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Diagnosis

***Escherichia coli* is the most common pathogen isolated from the urine of young women with acute cystitis, and it is present in 80% of cases (56).**

Staphylococcus saprophyticus is present in an additional 5% to 15% of patients with cystitis. The pathophysiology of cystitis in women involves the colonization of the vagina and urethra with coliform bacteria from the rectum. For this reason, the effects of an antimicrobial agent on the vaginal flora play a role in the eradication of bacteriuria.

Treatment

High concentrations of *trimethoprim* and *fluoroquinolone* in vaginal secretions can eradicate *E. coli* while minimally altering normal anaerobic and microaerophilic vaginal flora. An increasing linear trend in the prevalence of resistance of *E. coli* (9%–18%) to *trimethoprim* and *trimethoprim-sulfamethoxazole* has been noted. In contrast, no such increase in resistance was noted with *nitrofurantoin* and *ciprofloxacin*. *Nitrofurantoin* (macrocrystals, 100 mg orally twice daily for 7 days) or a *fluoroquinolone* (*ciprofloxacin*, 250 mg orally twice daily for 3 days) are the optimal choices for empirical 3-day therapy for uncomplicated cystitis (57).

In patients with typical symptoms, an abbreviated laboratory workup followed by empirical therapy is suggested. The diagnosis can be presumed if pyuria is detected by microscopy or leukocyte esterase testing. Urine culture is not necessary, and a short course of antimicrobial therapy should be given. No follow-up visit or culture is necessary unless symptoms persist or recur.

Recurrent Cystitis

About 20% of premenopausal women with an initial episode of cystitis have recurrent infections. More than 90% of these recurrences are caused by exogenous reinfection. Recurrent cystitis should be documented by culture to rule out resistant micro-organisms. Patients may be treated by one of three strategies: (i) continuous prophylaxis, (ii) postcoital prophylaxis, or (iii) therapy initiated by the patient when symptoms are first noted.

Postmenopausal women may also have frequent reinfections. **Hormonal therapy or topically applied estrogen cream, along with antimicrobial prophylaxis, is helpful in treating these patients.**

Urethritis

Women with dysuria caused by urethritis have a more gradual onset of mild symptoms, which

may be associated with abnormal vaginal discharge or bleeding related to concurrent cervicitis. Patients may also have a new sex partner or experience lower abdominal pain. Physical examination may reveal the presence of mucopurulent cervicitis or vulvovaginal herpetic lesions. *C. trachomatis*, *N. gonorrhoeae*, or genital herpes may cause acute urethritis. Pyuria is present on urinalysis, but hematuria is rarely seen. Treatment regimens for chlamydia and gonococcal infections are presented in Table 16.3.

Occasionally, vaginitis caused by *C. albicans* or trichomonas is associated with dysuria. On careful questioning, patients generally describe external dysuria, sometimes associated with vaginal discharge, and pruritus and dyspareunia. They usually do not experience urgency or frequency. Pyuria and hematuria are absent.

Acute Pyelonephritis

The clinical spectrum of acute, uncomplicated pyelonephritis in young women ranges from gram-negative septicemia to a cystitislike illness with mild flank pain. *E. coli* accounts for more than 80% of these cases (58). Microscopy of unspun urine reveals

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pyuria and gram-negative bacteria. A urine culture should be obtained in all women with suspected pyelonephritis; blood cultures should be performed in those who are hospitalized because results are positive in 15% to 20% of cases. In the absence of nausea and vomiting and severe illness, outpatient oral therapy can be given safely. Patients who have nausea and vomiting, are moderately to severely ill, and are pregnant should be hospitalized. Outpatient treatment regimens include *trimethoprim-sulfamethoxazole* (160–800 mg every 12 hours) or a quinolone (eg, *ofloxacin*, 200–300 mg every 12 hours) for 10 to 14 days. Inpatient treatment regimens include the use of parenteral *ceftriaxone* (1–2 g daily), *ampicillin* (1 g every 6 hours), and *gentamicin* (especially if *Enterococcus* species are suspected) or *aztreonam* (1 g every 8–12 hours). Symptoms should resolve after 48 to 72 hours. If fever and flank pain persist after 72 hours of therapy, ultrasound or computed tomography should be considered to rule out a perinephric or intrarenal abscess or ureteral obstruction. A follow-up culture should be obtained 2 weeks after the completion of therapy (58).

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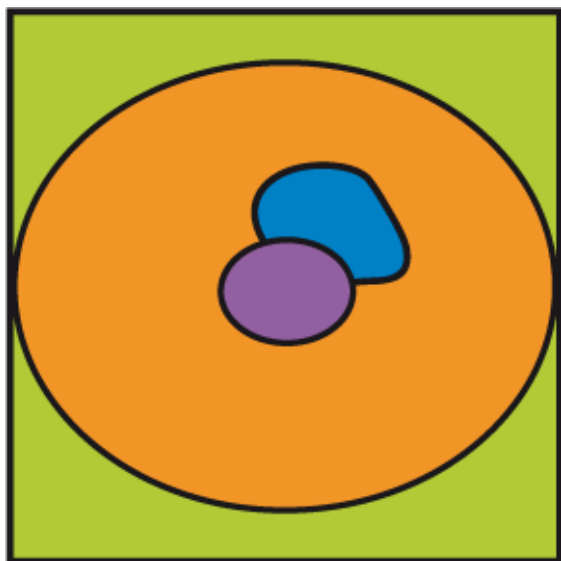
17

Intraepithelial Disease of the Cervix, Vagina, and Vulva

Ilana B. Addis

Kenneth D. Hatch

Jonathan S. Berek



- Cervical intraepithelial neoplasia (CIN) arises in an area of metaplasia in the transformation zone at the advancing squamocolumnar junction (SCJ) in most cases. Metaplasia advances from the original SCJ inward, toward the external os and over the columnar villi, which establishes an area called the *transformation zone*. CIN is most likely to begin either during menarche or after pregnancy, when metaplasia is most active; after menopause, metaplasia is less active and a woman has a lower risk of developing CIN.

- Most CIN 1 (and some CIN 2) lesions regress spontaneously if untreated; nevertheless, CIN refers to a lesion that may progress to invasive carcinoma. This term is equivalent to the term *dysplasia*, which means abnormal maturation; consequently, proliferating metaplasia without mitotic activity should not be called dysplasia. Squamous metaplasia should not be diagnosed as dysplasia (or CIN) because it does not progress to invasive cancer.

Approximately 90% of intraepithelial neoplasia is attributed to human papillomavirus (HPV) infection. Only certain types of HPV cause high-grade intraepithelial lesions and cancer (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, and -58). Type 16 is the most common form of HPV found in invasive cancer and in CIN 2 and CIN 3; it is found in 47% of women with cancer in these stages.

Potentially premalignant squamous lesions fall into three categories: (i) *atypical squamous cells (ASC)*, (ii) *low-grade squamous intraepithelial lesions (LSIL)*, and (iii) *high-grade squamous intraepithelial lesions (HSIL)*. The ASC category is subdivided into two categories: those of unknown significance (ASC-US) and those in which high-grade lesions must be excluded (ASC-H).

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The LSIL category includes CIN 1 (mild dysplasia) and the changes of HPV, termed *koilocytotic atypia*. The HSIL category includes CIN 2 and CIN 3 (moderate dysplasia, severe dysplasia, and carcinoma *in situ*).

The spontaneous regression rate of biopsy-proven CIN 1 is 60% to 85% in prospective studies. The regressions typically occur within a 2-year follow-up with cytology and colposcopy. For LSIL that persists for longer than 2 years, the choice of treatment is optional. Expectant management is still appropriate in some patients, and ablative therapies, including cryotherapy and laser ablation, are acceptable treatment modalities.

When a cytologic specimen suggests the presence of HSIL, colposcopy and directed biopsy should be performed. Although high-grade CIN can be treated with a variety of techniques, the preferred treatment for CIN 2 and 3 is loop electrosurgical excision procedure (LEEP).

Atypical endocervical cells pose a risk for adenocarcinoma *in situ* (AIS), which must be considered a serious cancer precursor of adenocarcinoma.

After sampling to rule out invasive disease, VAIN 3 lesions can be treated with laser therapy. Patients with vaginal intraepithelial neoplasia (VAIN) 1 (and possibly VAIN 2) and HPV infection do not require treatment. These lesions often regress, are multifocal, and recur quickly when treated with ablative therapy.

Vulvar intraepithelial neoplasia, grade 3 (VIN 3), is treated by simple excision, laser ablation, or superficial (partial) vulvectomy, with or without splitthickness skin grafting. Excision of small foci of disease produces excellent results, and although multifocal or extensive lesions may be difficult to treat by this approach, it offers the most cosmetic result. VIN 1-2 is also generally associated with dystrophic changes or HPV and can be managed expectantly.

Intraepithelial disease frequently occurs in the cervix, vagina, and vulva, and it may coexist in these areas. The cause and epidemiologic basis are common to all three locations, and treatment typically is ablative and conservative. Early diagnosis and management are essential to prevent disease from progressing to invasive cancer.

Cervical Intraepithelial Neoplasia

The concept of *preinvasive disease* of the cervix was introduced in 1947, when it was recognized that epithelial changes could be identified that had the appearance of invasive cancer but were confined to the epithelium (1). Subsequent studies showed that if these lesions are not treated, they can progress to cervical cancer (2). Improvements in cytologic assessment led to the identification of early precursor lesions called *dysplasia*, which signaled possible development of future cancer. For a number of years, carcinoma in situ (CIS) was treated very aggressively (most often with hysterectomy), whereas dysplasias were believed to be less significant and were not treated or were treated by colposcopic biopsy and cryosurgery. The concept of *cervical intraepithelial neoplasia* (CIN) was introduced in 1968, when Richart indicated that all dysplasias have the potential for progression (3). **It is now recognized that most CIN 1 (and some CIN 2) lesions regress spontaneously if untreated (4); nevertheless, CIN refers to a lesion that may progress to invasive carcinoma. This term is equivalent to the term *dysplasia*, which means abnormal maturation; consequently, proliferating metaplasia without mitotic activity should not be called dysplasia. Squamous metaplasia should not be diagnosed as dysplasia (or CIN) because it does not progress to invasive cancer.**

The criteria for the diagnosis of intraepithelial neoplasia may vary according to the pathologist, but the significant features are cellular immaturity, cellular disorganization, nuclear

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abnormalities, and increased mitotic activity. The extent of the mitotic activity, immature cellular proliferation, and nuclear atypicity identify the degree of neoplasia. If the mitoses and immature cells are present only in the lower one third of the epithelium, the lesion usually is designated as CIN 1. Involvement of the middle and upper thirds is diagnosed as CIN 2 and CIN 3, respectively (Fig. 17.1).

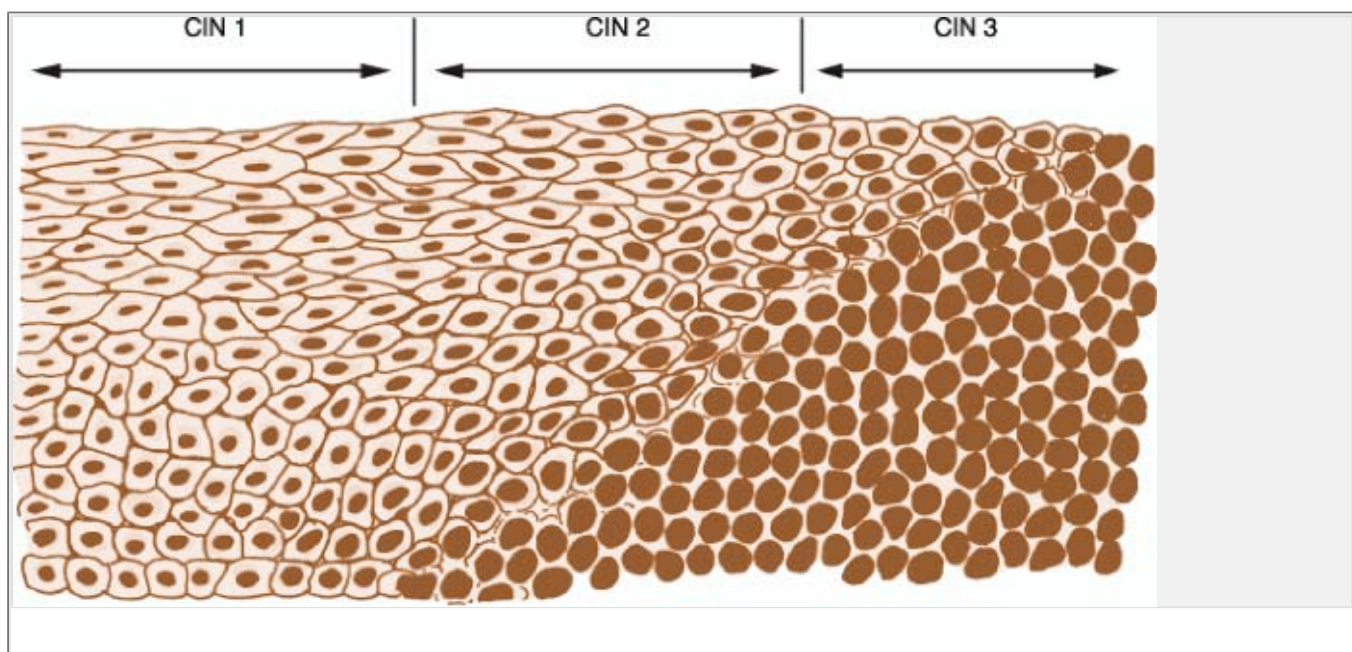


Figure 17.1 Diagram of cervical intraepithelial neoplasia compared with normal epithelium.

Cervical Anatomy

The cervix is composed of *columnar epithelium*, which lines the endocervical canal, and *squamous epithelium*, which covers the exocervix (5). The point at which they meet is called the *squamocolumnar junction* (SCJ) (Figs. 17.2 and 17.3).

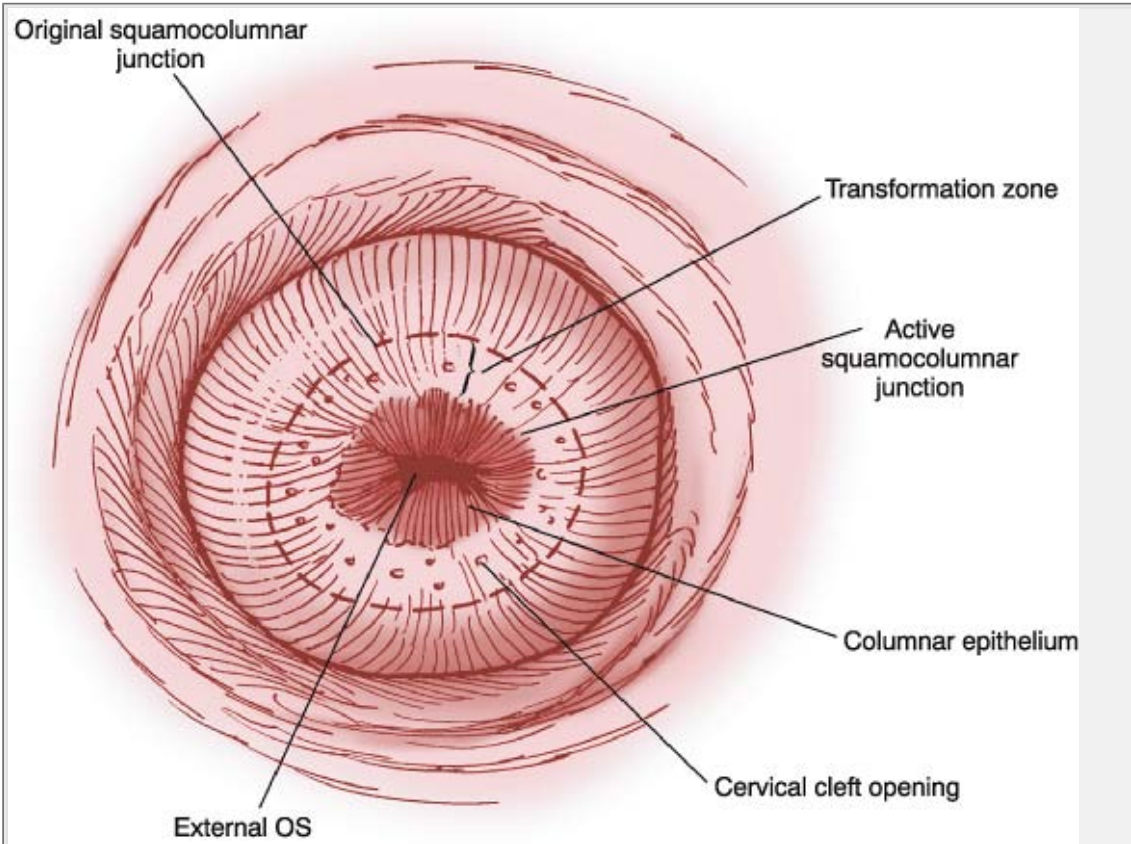


Figure 17.2 The cervix and the transformation zone.

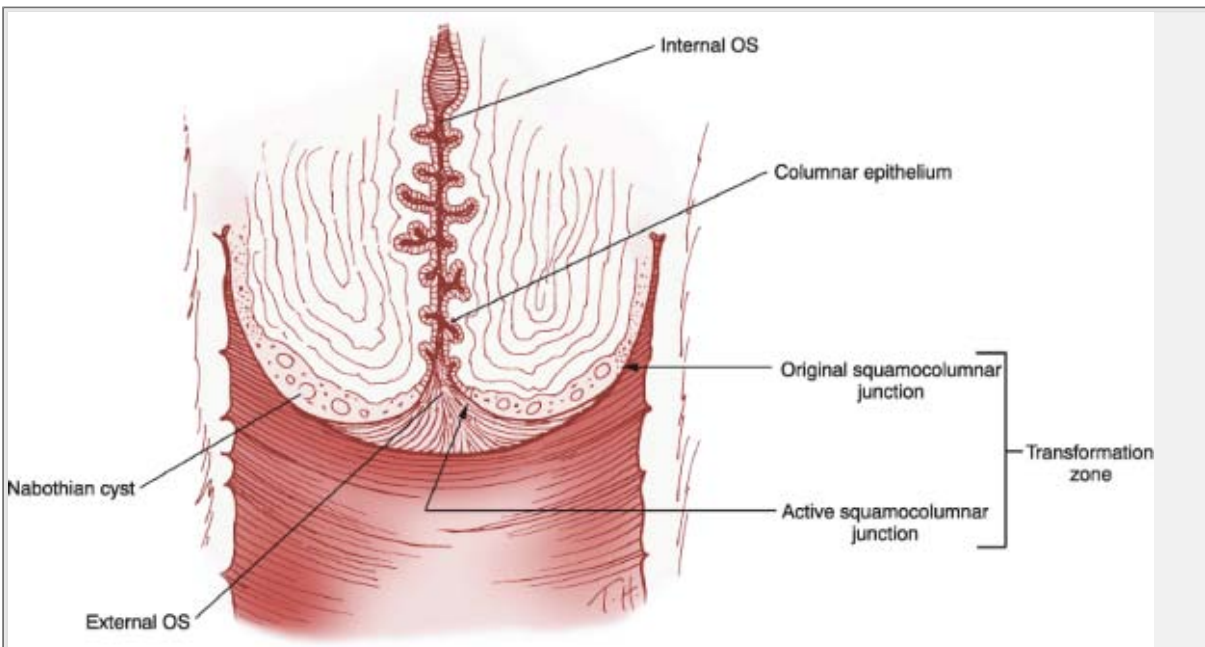


Figure 17.3 Diagram of the cervix and the endocervix.

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The Squamocolumnar

The SCJ rarely remains restricted to the external os. Instead, it is a dynamic point that **Junction** changes in response to puberty, pregnancy, menopause, and hormonal stimulation (Fig. 17.4). In neonates, the SCJ is located on the exocervix. At menarche, the production of estrogen causes the vaginal epithelium to fill with glycogen. Lactobacilli act on the glycogen to lower the pH, stimulating the subcolumnar reserve cells to undergo *metaplasia* (5).

Metaplasia advances from the original SCJ inward, toward the external os and over the columnar villi. This process establishes an area called the *transformation zone*. The transformation zone extends from the original SCJ to the physiologically active SCJ. As the metaplastic epithelium in the transformation zone matures, it begins to produce glycogen and eventually resembles the original squamous epithelium, colposcopically and histologically (Figs. 17.5a and b).

In most cases, CIN is believed to originate as a single focus in the transformation zone at the advancing SCJ. The anterior lip of the cervix is twice as likely to develop CIN as the posterior lip, and CIN rarely originates in the lateral angles. Once CIN occurs, it can progress horizontally to involve the entire transformation zone, but it usually does not replace the original squamous epithelium. This progression usually results in CIN with a sharp external border. Proximally, CIN involves the cervical clefts, and this area tends to have the most severe CIN lesions. The extent of involvement of these cervical glands has significant therapeutic implications because the entire gland must be destroyed to ensure elimination of the CIN (5). The only way to determine where the original SCJ was located is to look for nabothian cysts or cervical cleft openings, which indicate the presence of columnar epithelium. Once the metaplastic epithelium matures and forms glycogen, it is called the *healed* transformation zone and is relatively resistant to oncogenic stimuli. However, the entire SCJ with early metaplastic cells is susceptible to oncogenic factors, which may cause these cells to transform into CIN. Therefore, **CIN is most likely to begin either during menarche or after pregnancy, when metaplasia is most active. Conversely, after menopause a woman undergoes little metaplasia and is at a lower risk of developing CIN.** Oncogenic

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factors are introduced through sexual intercourse. Although several agents, including sperm, seminal fluid histones, trichomonas, chlamydia, and herpes simplex virus have been studied, it is now known that HPV plays an important role in the development of CIN.

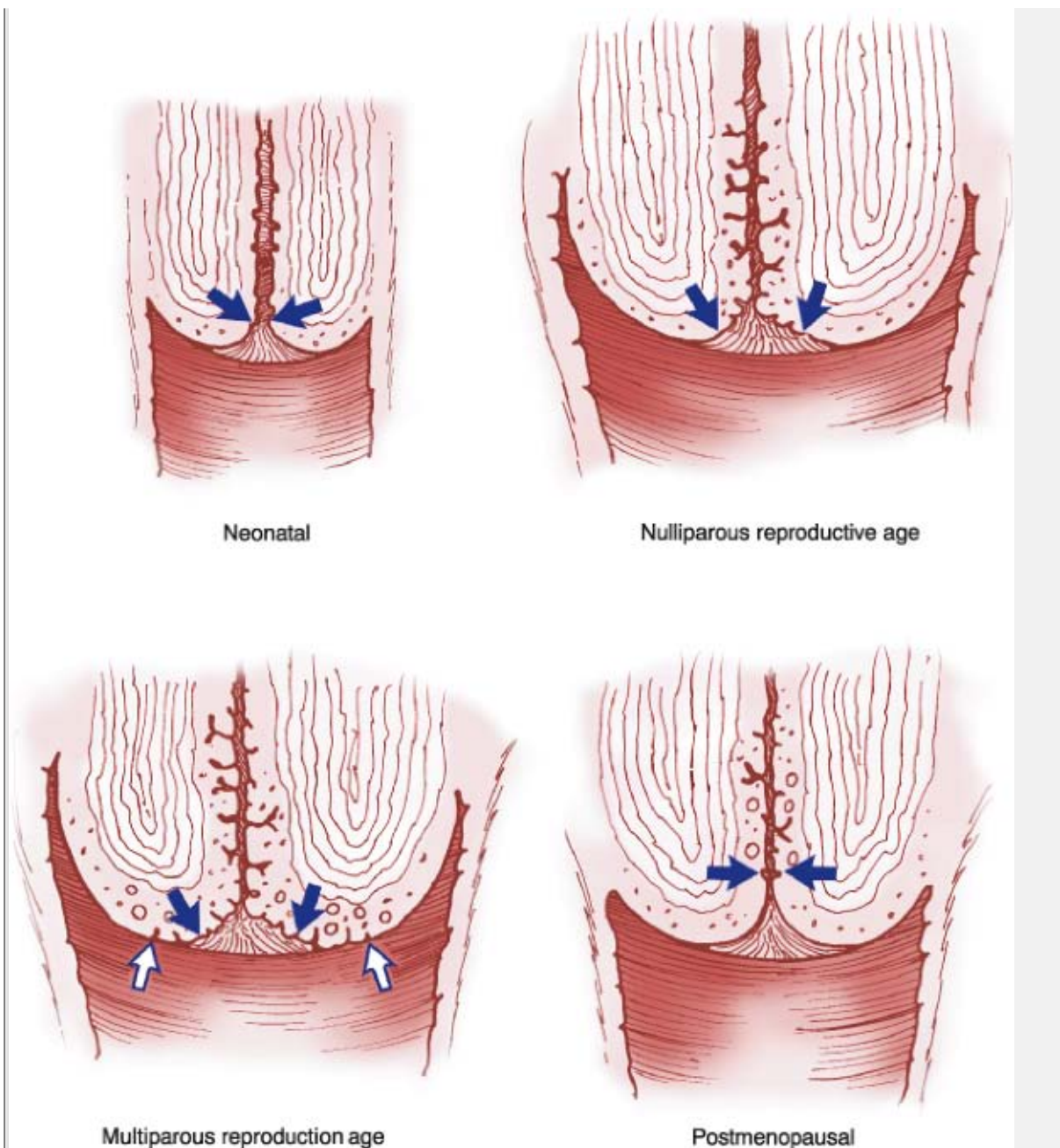


Figure 17.4 Different locations of the transformation zone and the squamocolumnar junction during a woman's lifetime. The arrows mark the active transformation zone.

Normal Transformation Zone

The original squamous epithelium of the vagina and exocervix has four layers (5):

- The *basal layer* is a single row of immature cells with large nuclei and a small amount of cytoplasm.
- The *parabasal layer* includes two to four rows of immature cells that have normal mitotic figures and provide the replacement cells for the overlying epithelium.

The *intermediate layer* includes four to six rows of cells with larger amounts of cytoplasm in a polyhedral shape separated by an intercellular space. Intercellular bridges, where differentiation of glycogen production occurs, can be identified with light microscopy.

The *superficial layer* includes five to eight rows of flattened cells with small uniform nuclei and a cytoplasm filled with glycogen. The nucleus becomes pyknotic, and the cells detach from the surface (exfoliation). These cells form the basis for Papanicolaou (Pap) testing.



Figure 17.5 A: Active metaplasia in the transformation zone. B: Maturing metaplasia in the transformation zone.

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Columnar Epithelium Columnar epithelium has a single layer of columnar cells with mucus at the top and a round nucleus at the base. The glandular epithelium is composed of numerous ridges, clefts, and infoldings and, when covered by squamous metaplasia, leads to the appearance of gland openings. Technically, the endocervix is not a gland, but the term *gland openings* often is used.

Metaplastic Epithelium Metaplastic epithelium, found at the SCJ, begins in the subcolumnar reserve cell (Fig. 17.4). Under stimulation of lower vaginal acidity, the reserve cells proliferate, lifting the columnar epithelium. The immature metaplastic cells have large nuclei and a small amount of cytoplasm without glycogen. As the cells mature normally, they produce glycogen, eventually forming the four layers of epithelium. The metaplastic process begins at the tips of the columnar villi, which are exposed first to the acid vaginal environment. As the metaplasia replaces the columnar epithelium, the central capillary of the villus regresses, and the epithelium flattens out, leaving the epithelium with its typical vascular network. As metaplasia proceeds into the cervical clefts, it replaces columnar epithelium and similarly flattens the epithelium. The deeper clefts, however, may not be completely replaced by the metaplastic epithelium, leaving mucus-secreting columnar epithelium trapped under the squamous epithelium. Some of these glands open onto the surface; others are completely encased, with mucus collecting in nabothian cysts. Gland openings and nabothian cysts mark the original SCJ and the outer edge of the original transformation zone (5) (Figs 17.5a and b).

Human Papillomavirus

The cytologic changes of HPV were first recognized by Koss and Durfee (6) in 1956 and given the term *koilocytosis*. Their significance was not recognized until 20 years later, when Meisels and colleagues (7) reported these changes in mild dysplasia (Fig. 17.6). Molecular biologic studies have shown high levels of HPV DNA and capsid antigen, indicating

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productive viral infection in these koilocytic cells (8). The HPV genome has been found in all grades of cervical neoplasia (9). Infection with HPV is the primary cause of cervical cancer (10). As the CIN lesions become more severe (Fig. 17.7), the koilocytes disappear, the HPV copy numbers decrease, and the capsid antigen disappears, indicating that the virus is not capable of reproducing in less differentiated cells (11). Instead, portions of the HPV DNA become integrated into the host cell. Integration of the transcriptionally active DNA into the host cell appears to be essential to malignant growth (12). **Malignant transformation requires the expression of E6 and E7 oncoproteins produced by HPV** (13). Because HPV will not grow in cell culture, there is no direct evidence of the carcinogenesis of HPV. However, a cell culture system for growing keratinocytes has been described that allows for stratification and differentiation of specific keratinase types (14). When normal cells are transfected with the plasmid-containing HPV-16, the transfected cells produced cytologic abnormalities identical to those seen in intraepithelial neoplasia. The E6 and E7 oncoproteins are identifiable in the transfected cell lines, providing strong laboratory evidence of a cause-and-effect relationship (15). Cervical cancer cell lines that contain active copies of HPV-16 or -18 (SiHa, HeLa, C 4-11, Ca Ski) show the presence of HPV-16 E6 and E7 oncoproteins (16).

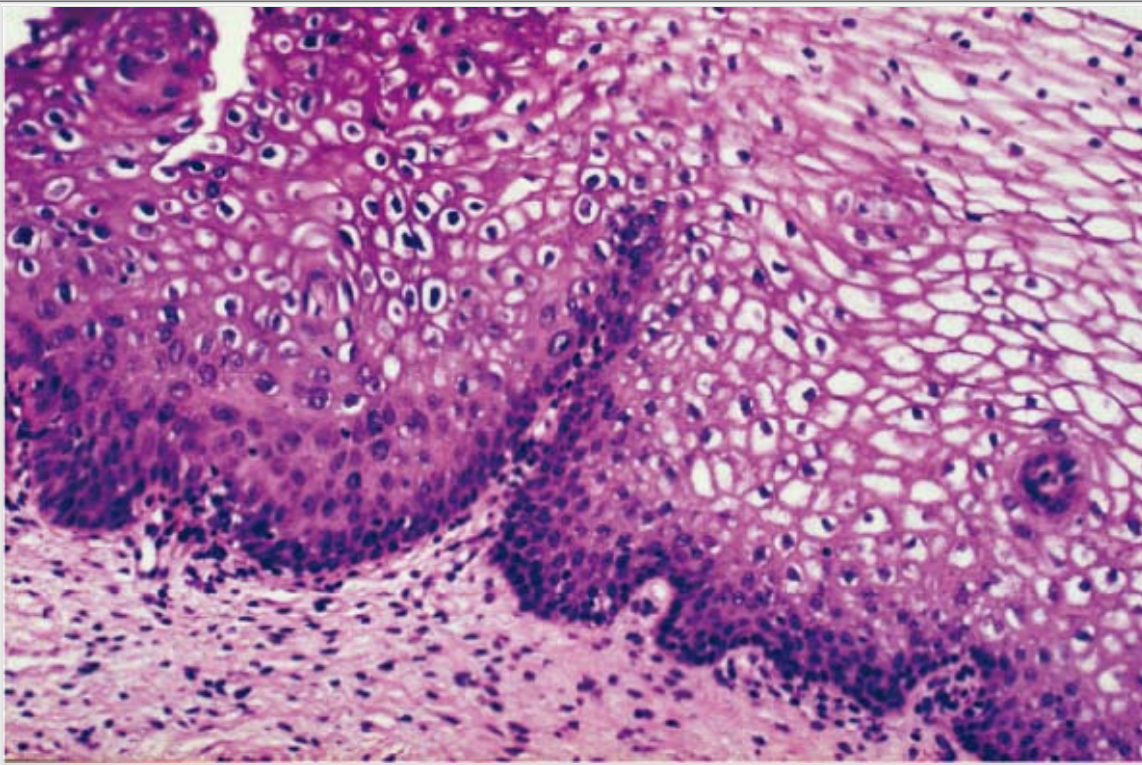


Figure 17.6 Cervical intraepithelial neoplasia grade 1 with koilocytosis. The normal maturation process and differentiation from the basal and parabasal layers to the intermediate and superficial layers are maintained. In the upper layers, koilocytes are characterized by perinuclear halos, well-defined cell borders, and nuclear hyperchromasia, irregularity, and enlargement.

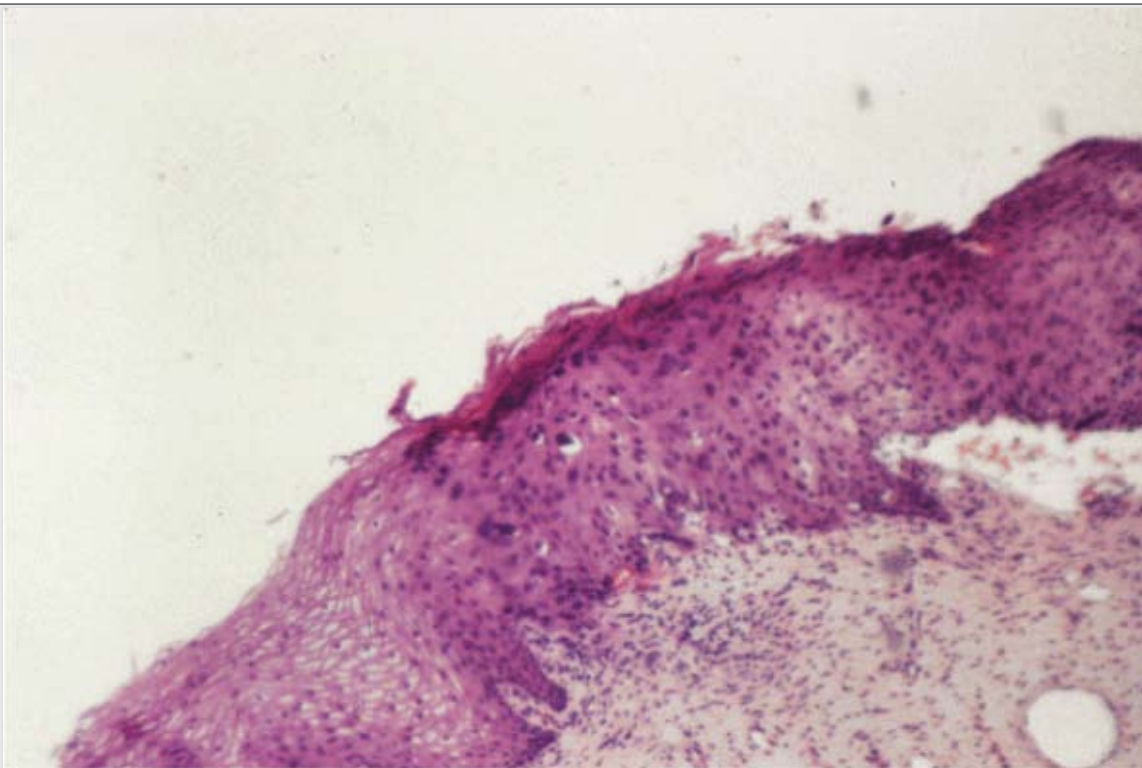


Figure 17.7 Cervical biopsy showing normal cells, CIN 2, and CIN 3. In CIN 3, the normal maturation is lost.

HPV DNA can be detected in most women with cervical neoplasia (17,18). There have been more than 120 types of HPV identified, with 30 of these HPV types primarily infecting the squamous epithelium of the lower anogenital tract of men and women (19,20). Detection of HPV is associated with a 250-fold increase risk of high-grade CIN (21). **The percentage of intraepithelial neoplasia attributed to HPV infection approaches 90% (18).**

Only certain types of HPV count for about 90% of high-grade intraepithelial lesions and cancer (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, and -58) (18). Type 16 is the most common HPV found in invasive cancer and in CIN 2 and CIN 3, and it is found in 47% of women with cancer in these stages (22). It is also the most common HPV type found in women with normal cytology.

Unfortunately, HPV-16 is not very specific; it can be found in 16% of women with low-grade lesions and in up to 14% of women with normal cytology. **Human papillomavirus type-18**

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is found in 23% of women with invasive cancers, 5% of women with CIN 2 and CIN 3, 5% of women with HPV and CIN 1, and fewer than 2% of patients with negative findings (18). Therefore, HPV-18 is more specific than HPV-16 for invasive tumors.

Usually, HPV infections do not persist. Those that do persist can remain latent for many years. Most women have no clinical evidence of disease, and the infection is eventually suppressed or eliminated (17). Other women exhibit low-grade cervical lesions that may regress spontaneously. **In most women, the infection will clear in 9 to 15 months (23).** A minority of women exposed to HPV develop persistent infection that may progress to CIN (17,24). Persistent high-risk HPV infection increases the risk of high-grade disease 300-fold and is required for the development and maintenance of CIN 3 (25,26). Factors that may have a role in this progression include smoking, contraceptive use, infection with other sexually transmitted diseases, or nutrition (17,22). Any factor that influences the integration of HPV DNA into the human genome may cause progression to invasive disease (27).

Human Papillomavirus Vaccine Development

Historically, vaccines have represented a cost-effective method for preventing disease induced by microbial agents and other pathogens. The **development of a vaccine for HPV** could lead to a potential reduction in the incidence of cervical cancer and its precursor lesions, other associated cancers (anal, penile, vaginal, vulvar), and genital warts (28). Recently **three separate trials have been performed to test the efficacy of various HPV vaccines. Each trial was able to show that the vaccine they were using was efficacious in preventing persistent HPV infection.** In a randomized trial of an experimental HPV-16 VLP vaccine 1,533 women were randomized to either the vaccine or placebo. Each subject had no history of abnormal Pap test results and no more than five male sexual partners. The vaccine was given at day 0, month 2, and month 6, and the median follow-up period was 17.4 months. The primary endpoint to this trial was persistent HPV-16 infection, and the secondary endpoint was the tolerability of the vaccine. This trial found that there was a decrease in persistent and transient HPV-16 infection as well as in cases of CIN in vaccinated versus placebo subjects (29).

Another trial of a bivalent L1 VLP vaccine for the prevention of HPV-16 and -18 used a similar protocol. Women were enrolled if they had a history of no more than six sexual partners and no history of abnormal Pap test results. They also had to test negative cytologically for the high-risk HPV types. The primary objective was to assess the effectiveness of the vaccine in the prevention of infection with HPV-16 and -18, and the secondary objective was to assess its efficacy in prevention of cytologic and histologic abnormalities and cancer. The 1,113 participants were followed for 27 years. **The results of this trial found that the efficacy of the vaccine was more than 85% for persistent infection and 93% for**

cytologic abnormalities (30).

In a phase 2 trial of a quadrivalent HPV vaccine, the primary endpoints were persistent HPV infection, any type of intraepithelial neoplasia, genital tract cancer, and external genital lesions. In an intention-to-treat analysis, the overall efficacy of the vaccine was 89%. The conclusions of this phase 2 trial were that the vaccine was highly effective in reducing the incidence of persistent HPV infection. The study did not, however, have enough power to assess vaccine efficacy for the disease endpoints or for each HPV type separately. This study also found that the vaccine was highly immunogenic and induced high antibody titers to each HPV type (31).

Papanicolaou Test

In 1988, the first National Cancer Institute (NCI) workshop held in Bethesda, Maryland, **Classification** resulted in the development of the Bethesda System for cytologic reporting (32). A standardized method of reporting cytology findings was needed to facilitate peer review and quality assurance. **The terminology was refined in the Bethesda III System (2001). According to this system, potentially premalignant squamous lesions fall into three**

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categories: (i) *atypical squamous cells (ASC)*, (ii) *low-grade squamous intraepithelial lesions (LSIL)*, and (iii) *high-grade squamous intraepithelial lesions (HSIL)* (33). The ASC category is subdivided into two categories: those of unknown significance (ASCUS), and those in which high-grade lesions must be excluded (ASC-H). Low-grade squamous intraepithelial lesions include CIN 1 (mild dysplasia) and the changes of HPV, termed *koilocytotic atypia*. The HSIL category includes CIN 2 and CIN 3 (moderate dysplasia, severe dysplasia, and carcinoma *in situ*). A comparison of the various terms as they relate is shown in Table 17.1.

<i>Bethesda System</i>	<i>Dysplasia/CIN System</i>	<i>Papanicolaou System</i>
Within normal limits	Normal	I
Infection (organism should be specified)	Inflammatory atypia (organism)	II
Reactive and reparative changes		
Squamous cell abnormalities	Squamous atypia	IIR
Atypical squamous cells (1) of undetermined significance (ASC-US)	HPV atypia, exclude LSIL	
(2) exclude high-grade lesions (ASC-H)	Exclude HSIL HPV atypia	
Low-grade squamous intraepithelial lesion (LSIL)	Mild dysplasia CIN 1	
High-grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia CIN 2	III
	Severe dysplasia CIN 3 Carcinoma <i>in situ</i>	IV
Squamous cell carcinoma	Squamous cell carcinoma	V
CIN, cervical intraepithelial neoplasia, HPV, human papillomavirus.		

Cellular changes associated with HPV (ie, koilocytosis and CIN 1) are incorporated within

the category of LSIL because the natural history, distribution of various HPV types, and cytologic features of both of these lesions are the same (27). **Long-term follow-up studies have shown that lesions properly classified as koilocytosis progress to high-grade intraepithelial neoplasia in 14% of cases (33) and that lesions classified as mild dysplasia progress to severe dysplasia or CIS in 16% of cases (4).** It was initially thought that lesions classified as koilocytosis would contain only low-risk HPV types, such as HPV-6 and -11, whereas high-risk HPV types, such as HPV-16 and -18, would be limited to true neoplasms, including CIN 1, thus justifying the distinction. Histopathologic and molecular virologic correlation, however, has shown a similar heterogeneous distribution of low and high-risk HPV types in both koilocytosis and CIN 1 (34). Studies evaluating the dysplasia, CIS, and CIN terminology have had a lack of interobserver and intraobserver reproducibility (35). The greatest lack of reproducibility is between koilocytosis and CIN 1 (36). **Thus, on the basis of clinical behavior, molecular biologic findings, and morphologic features, HPV changes and CIN 1 appear to be the same disease.** The rationale for combining CIN 2 and CIN 3 into the category of HSIL is similar. The biologic studies reveal the similar mix of high-risk HPV types in the two lesions, and the separation of the lesions has been shown to be irreproducible (35,36). In addition, the management of CIN 2 and CIN 3 is similar.

Diagnosis

The Papanicolaou Test

The Pap test has been successful in reducing the incidence of cervical cancer by 79% and the mortality by 70% since 1950 (37). Unfortunately, 20% of women in the

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United States do not undergo regular screening and have not had a Pap test in the previous 3 years. Recently the annual incidence rate has dropped from 8 to 5 cases per 100,000 women. This means that approximately 8,200 women per year are acquiring cervical cancer (37,38,39). Cases of cervical cancer continue to occur in patients who have had regular Pap tests. The Agency for Health Care and Policy Research, now renamed the Agency for Healthcare Research and Quality (AHRQ), undertook a literature review of conventional cervical cytology testing techniques and compared them with newer technologies designed to reduce the false-negative rate (40). For this project, five reports were analyzed, and the conclusion was that the sensitivity of conventional cytologic testing in detecting cervical cancer precursor lesions was 51%. This is a false-negative rate of 49%. **In three recent reviews of the accuracy of cervical cytology assessment, the sensitivity of the Pap test in detecting CIN 2–3 ranged from 47% to 62% and the specificity ranged from 60% to 95% (41,42,43). Approximately 30% of new cancer cases each year result from women who have undergone Pap testing, but errors of sampling, fixation, or interpretation occur (44).** Previously, it had been widely believed that sensitivity of the Pap test was in the 80% range (45). Recommendations for Pap test screening were based on this perceived 80% sensitivity. The recommendation that three annual Pap tests be performed is predicated on a false-negative rate that would reduce the risk for missed lesions to less than 1% after the first three tests. If the test sensitivity were 80%, then the sensitivity of three negative tests would be 99.2%, which achieves the screening goal. However, the 51% test sensitivity would have a sensitivity of only 86.8% after three tests.

It is obvious that improvement in the conventional Pap test technique is necessary. Falsenegative errors occur in sampling, preparation, and interpretation. Sampling errors occur because a lesion is too small to exfoliate cells or the device used did not pick up the cells and transfer them to the glass slide. Preparation errors may occur because of poor fixation on

the glass slide, leading to air-drying and an inability to interpret the results. The slide may also be too thick and obscured by vaginal discharge, blood, or mucus. The thick slide also leads to poor fixation because the fixative does not penetrate the cell sample. Interpretive errors occur when the slide contains diagnostic cells that the screening technician did not identify.

Using a liquid-based medium to collect the cytologic sample and preserve the collected cervical cells can alleviate sampling and preparation errors. The sample is then processed to provide a uniform, thin layer of cervical cells without debris on a glass slide. The AHRQ reported that liquid-based cytology assessment improved the sensitivity of the Pap test to the stated goal of 80%. The cell sample is collected with an endocervical brush used in combination with a plastic spatula or with a plastic broom. The sample is then rinsed in a vial containing liquid preservative. With this technique, 80% to 90% of the cells are transferred to the liquid media, as compared with the only 10% to 20% transferred to the glass slide with conventional cytologic testing. In addition, using liquid-based media eliminates air-drying. The cells are retrieved from the vial by passing the liquid through a filter, which traps the larger epithelial cells, separating them from the small blood and inflammatory cells. This process leads to a thin layer of diagnostic cells properly preserved and more easily interpreted by the cytologist. This technique reduces by 70% to 90% the rate of unsatisfactory samples encountered with conventional cytologic testing (46). Liquid-based cytology is now commonly performed by most of the laboratories in the United States.

A second new technology for assessment of cervical cytology is the AutoPap Screening System, which has been approved by the U.S. Food and Drug Administration for primary screening and rescreening of samples initially interpreted as normal. This technique uses an automated microscope coupled to a special digital camera. The system scans the slide and uses computer imaging techniques to analyze each field of view on the slide. Computer algorithms are then used to rank each slide on the basis of the probability that the sample may contain an abnormality. The selected slides are then reviewed by a cytotechnologist or a cytopathologist. This technique has reduced the false-negative rate by 32% (47). The AutoPap Screening System currently is not in widespread use.

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The Bethesda System for reporting the results of cervical cytology was developed as a uniform system of cytology that would provide clear guidance for clinical management (32). It creates a standardized framework for laboratory reports that include a descriptive diagnosis and an evaluation of specimen adequacy. The Bethesda System has been modified to reflect the development of new technologies and research findings.

In the 2001 Bethesda System, specimen adequacy is categorized as *satisfactory* or *unsatisfactory* for evaluation. If a specimen is found to be unsatisfactory, cervical cytology is repeated in 2 to 4 months. The category *satisfactory but limited by* has been eliminated from the new system; however, if sampling of the transformation zone is inadequate or obscuring factors are present, cervical cytology can be repeated in 6 to 12 months. The general categorizations are (i) negative for intraepithelial lesion or malignancy, (ii) epithelial cell abnormality, and (iii) other. In the category of *negative for intraepithelial lesions or malignancy* are included organisms such as *trichomonas vaginalis*, candida, bacterial vaginosis, as well as actinomyces and herpes simplex virus. Also included in this category are reactive cellular changes, glandular cells status after hysterectomy, and atrophy. The category *epithelial cell abnormality* includes squamous cell and glandular cell abnormalities. The atypical squamous cell group differs from the 1992 guidelines in that ASCUS has been modified and that the term *atypical squamous cells favor reactive* has been eliminated. **Atypical squamous cells are divided into *undetermined significance (ASC-US)* and *cannot exclude high-grade squamous intraepithelial lesion (ASC-H)*. *Lowgrade squamous intraepithelial lesion***

(LSIL) encompasses HPV and CIN 1. High-grade squamous intraepithelial lesion (HSIL) includes CIN 2 and 3 and CIS.

The glandular cell group has changed from the 1992 guidelines in that the designation of *atypical glandular cells of undetermined significance* (AGUS) has been eliminated in favor of more descriptive groupings of atypical glandular cells. **The group of glandular cell abnormalities includes atypical glandular cells (AGC) endocervical, endometrial, or glandular cells not otherwise specified; and atypical glandular cells (endocervical or glandular) favor neoplasia** (Table 17.2).

Screening Guidelines

Recommendations for cervical cancer screening are slightly conflicting. The **American Cancer Society (ACS) updated recommendations** of 2002 states that screening with conventional Pap testing should occur every year. If liquid-based cytology is being used, screening can be extended to every 2 years. **Screening should begin at the age of 21 or within 3 years of the onset of sexual activity, and screening can stop at age 70 if there has been no abnormal Pap test result in the past 10 years. The ACS also states that screening after hysterectomy for benign disease is not necessary** (48).

The American College of Obstetricians and Gynecologists (ACOG) differs from the ACS recommendations by stating that women younger than the age of 30 should undergo cervical cytology screening yearly, and those older than the age of 30 without any other risk factors (history of CIN 2 or 3, immunocompromised, diethylstilbestrol exposure *in utero*) can extend their screening interval to 2 to 3 years using either liquid-based or conventional Pap testing. Furthermore, ACOG states that using combination cervical cytology and HPV DNA screening is appropriate for women age 30 and older. If results are negative using this combination, a woman can be retested at only 3-year intervals (49) (Table 17.3).

In 2003, the U.S. Food and Drug Administration approved **HPV DNA testing combined with cervical cytology as a screening technique for women older than age 30. When the results of both tests are negative, the woman does not have to be retested for 3 years. The negative predictive value of a double negative test exceeds 99%** (19).

Because most HPV infections are transient, clear spontaneously, and do not lead to real cancer precursors, especially in young women where the prevalence is higher, it should not be used for screening in women younger than 30 (50). Women who have negative test

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results for both cytology and HPV have a 1 in 1,000 chance of having CIN 2 or worse detected in the following 6 months (51). Prospective studies report less than 2 per 1,000 women will develop CIN 2 or greater in the following 3 years (51,52,53). This high negative predictive value allows for the screening interval to be extended to 3 years, which is supported by both ACOG and the American Cancer Society (ACS).

Table 17.2 Bethesda System 2001

Specimen Type: Indicate conventional smear (Pap smear) vs. liquid based vs. other

Specimen Adequacy

- Satisfactory for evaluation (*describe presence or absence of endocervical/transformation zone component and any other quality indicators, eg, partially obscuring blood, inflammation, etc.*)
- Unsatisfactory for evaluation ... (*specify reason*)
 - Specimen rejected/not processed (*specify reason*)
 - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

General Categorization (*optional*)

- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality: See Interpretation/Result (*specify "squamous" or "glandular" as appropriate*)
- Other: See Interpretation/Result (*eg, endometrial cells in a woman 40 years of age*)

Automated Review

If case examined by automated device, specify device and result.

Ancillary Testing

Provide a brief description of the test methods and report the result so that it is easily understood by the clinician.

Interpretation/Result

Negative for Intraepithelial Lesion or Malignancy (*when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report, whether or not there are organisms or other nonneoplastic findings*)

Organisms

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* spp.
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces* spp.
- Cellular changes consistent with herpes simplex virus

Other Nonneoplastic Findings (*optional to report; list not inclusive*):

- Reactive cellular changes associated with:
 - inflammation (includes typical repair)
 - radiation
 - intrauterine contraceptive device (IUD)
- Glandular cells status posthysterectomy
 - Atrophy

Other

- Endometrial cells (*in a woman 40 years of age*)
(*specify if "negative for squamous intraepithelial lesion"*)

Epithelial Cell Abnormalities

Squamous Cell

- Atypical squamous cells
 - of undetermined significance (ASC-US)
 - cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV/mild dysplasia/CIN 1
- High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, CIS/CIN 2 and CIN 3
 - with features suspicious for invasion (*if invasion is suspected*)
- Squamous cell carcinoma

Glandular Cell

- Atypical
 - endocervical cells (not otherwise specified [NOS] *or specify in comments*)
 - endometrial cells (NOS *or specify in comments*)
 - glandular cells (NOS *or specify in comments*)
- Atypical
 - endocervical cells, favor neoplastic
 - glandular cells, favor neoplastic
- Endocervical adenocarcinoma *in situ*
- Adenocarcinoma
 - endocervical
 - endometrial
 - extrauterine
 - NOS

Other Malignant Neoplasms (*specify*)

Educational Notes and Suggestions (*optional*)

Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).

Solomon D, Davey D, Kurman R, et al. *The 2001 Bethesda System: terminology for reporting results of cervical cytology.* JAMA2002; 287: 2114–2119.

Available at: <http://www.bethesda2001.cancer.gov>.

Atypical Squamous Cells

The ASC category is restricted to those test results disclosing abnormal cells that are truly of unknown significance. The ASC category does not include benign, reactive, and reparative changes that should be classified as normal in the Bethesda system. Because of the lack of diagnostic criteria and the fear of medical–legal action, the diagnosis has become quite common, ranging from 3% to 25% in some centers (54). When standardized diagnostic criteria are used, the rate of ASC results should be 3% to 5% (55). **The older term, ASCUS (Bethesda II classification) is now subdivided into ASC-US and ASC-H (Bethesda III classification).**

Table 17.3 Comparison of Screening Guidelines from the American Cancer Society and the American College of Obstetricians and Gynecologists

<i>Comparison of Cervical Cytology Screening</i>		
<i>Guideline</i>	<i>American Cancer Society</i>	<i>American College of Obstetricians and Gynecologists</i>
<i>Initial screening</i>	<ul style="list-style-type: none"> • Age 21 or 3 y after vaginal sex 	<ul style="list-style-type: none"> • Age 21 or 3 y after vaginal sex
<i>Interval</i>	<ul style="list-style-type: none"> • Every year for conventional Pap • Every 2 years for liquid-based Pap • Every 2–3 y after age 30 with 3 consecutive normals 	<ul style="list-style-type: none"> • Every year for either liquid-based Pap or conventional • Every 2–3 y after age 30 with 3 consecutive normals
<i>Discontinue</i>	<ul style="list-style-type: none"> • Age 70 if 3 consecutive normals in 10 y 	<ul style="list-style-type: none"> • No upper limit of age

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The cytologic diagnosis of ASC-US is associated with a 10% to 20% incidence of CIN 1 and a 3% to 5% risk for CIN 2 or 3 (56,57,58,59). It has become apparent that CIN 1 is most often a benign HPV infection and will regress spontaneously in more than 60% of cases (60); therefore, the goal of triage of an AS-CUS Pap test result is to identify more advanced CIN 2 and 3 lesions.

Triage options include the following: (i) Repeat Pap test every 4 to 6 months with referral for colposcopy if any subsequent abnormality is detected, (ii) immediate colposcopy, and (iii) HPV testing.

The option of repeat Pap testing is weakened by the 20% to 50% false-negative rate in identifying CIN lesions as well as the noncompliance of the patient. About 50% of patients will still undergo colposcopy because of subsequent abnormal Pap test results, making this option nearly as costly as immediate colposcopy (56). **Immediate colposcopy is assumed to be the most sensitive method of detecting CIN 2 or 3 (56,59).** Because 80% of patients will not have significant lesions, it is important to avoid overinterpretation of the colposcopic findings and to be conservative in performing biopsies. There is also the risk that pathologists will overinterpret the biopsy results and the patient will be diagnosed with CIN when metaplasia is the only finding.

Several studies have documented the usefulness of HPV testing in the assessment of ASC-US Pap test results (61,62,63). These studies have shown that HPV testing can identify 90% of the patients with CIN 2 or 3 lesions. To compare the aforementioned triage method in a prospective, randomized fashion, the NCI funded an ASC-US/LSIL Triage Study (ALTS) (64). Patients with ASC-US or LSIL were randomized to three triage arms: (i) immediate colposcopy, (ii) HPV test, and (iii) conservative management by repeat Pap test. There were 1,163 women in the immediate colposcopy group, and 14 refused the examination. The results of colposcopy are assumed to reflect the prevalent disease rates, which were as follows: CIN 1, 14.3%; CIN 2, 16.1%; and CIN 3, 5%. Thus, 75% of the women with ASC-US had negative colposcopy results and either did not have a biopsy (25%) or had a biopsy with negative results. The HPV test results were positive in 56.1% of the patients, and 6.1% of the patients did not return for colposcopy. Of the 494 who underwent colposcopy, the results were as follows: CIN 1, 22.5%; CIN 2, 11.9%; and CIN 3, 15.6%. The sensitivity of HPV test was 95.9% for the detection of CIN 2 and 96.3% for the detection of CIN 3.

In the conservatively managed group, only one follow-up Pap test was reported. To be effective, it is recognized that Pap testing must be done every 6 months. Despite this, the results of the

single follow-up Pap test were included. Using a cutoff that includes any positive finding of ASC-US or greater, the sensitivity is 85% for CIN 2 and 85.3% for CIN 3, with 58.6% of patients being referred for colposcopy. If LSIL is used as a cutoff, 26.2% of the patients are referred, with sensitivity of 64.0% for both CIN 2 and 3. Using HSIL as the cutoff, 6.9% are referred, and the sensitivity falls to 44%.

The conclusion of the ALTS trial is that HPV triage is highly sensitive in identifying CIN 2 and 3 lesions and that it cuts the rate of referral for colposcopy by approximately one half. Although the final cost-utility analysis of ALTS data is not complete, HPV testing seems to be an appropriate strategy for the initial management of ASC-US (65). When mathematical models are used to simulate the natural history of HPV and cervical cancer in a cohort of U.S. women, a 2- to 3-year screening strategy that uses cytologic assessment in combination with either HPV DNA testing or reflex HPV testing should be more effective in reducing the rate of cancer and be less costly than annual conventional cytology (66).

In 2001, the **American Society for Colposcopy and Cervical Pathology (ASCCP) sponsored an NCI Consensus Conference** to provide guidelines for the management of abnormal cervical cytology. Researchers used information from the ALTS Trial and Bethesda III terminology. **They recommended that women with ASC-US should be**

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managed with (i) a program of two repeat Pap tests with referral of any abnormality to colposcopy, (ii) immediate colposcopy, and (iii) testing for high-risk type HPV. Testing for HPV DNA is the preferred method when liquid-based cytology is used. Women who have positive test results should be referred for colposcopy, and those who are negative should receive yearly cytology assessment (62).

Low-grade Squamous Intraepithelial Lesions

The cytologic diagnosis of LSIL is reproducible and accounts for 1.6% of cytologic diagnoses (55). About 75% of the patients have CIN, with 20% being CIN 2 or 3 (56,57,58). These patients require additional evaluation. The ALTS trial closed the HPV test arm early because the HPV positivity rate was 82% and, therefore, was not a valid discriminator in determining the presence of disease. The ALTS trial found that a cytology interpretation of LSIL is associated with a 25% risk of histologic CIN grade 2 or 3 within 2 years. However, no effective triage strategy was identified to spare many women from colposcopic referral without increasing their risk of CIN 3 and invasive carcinoma (67). **The ALTS trial confirmed the validity of the current practice of performing colposcopy to evaluate a single LSIL result.**

High-grade Squamous Intraepithelial Lesions

Any woman with a cytologic specimen suggesting the presence of HSIL should undergo colposcopy and directed biopsy. After colposcopically directed biopsy and determination of the distribution of the lesion, ablative therapy and destruction of the entire transformation zone should be performed.

Colposcopy Findings

Acetowhite Epithelium Epithelium that turns white after application of acetic acid (3%–5%) is called *acetowhite epithelium* (40). **The application of acetic acid coagulates the proteins of the nucleus and cytoplasm and makes the proteins opaque and white (5).**

The acetic acid does not affect mature, glycogen-producing epithelium because the acid does not penetrate below the outer one third of the epithelium. The cells in this region have very

small nuclei and a large amount of glycogen (not protein). These areas appear pink during colposcopy. Dysplastic cells are those most affected. They contain large nuclei with abnormally large amounts of chromatin (protein). The columnar villi become "plumper" after acetic acid is applied; these cells are then easier to see. They appear slightly white, particularly in the presence of the beginning signs of metaplasia. The immature metaplastic cells have larger nuclei and also show some effects of the acetic acid. Because the metaplastic epithelium is very thin, it is not as white or opaque as CIN but instead appears gray and filmy (5).

Leukoplakia Translated literally, *leukoplakia* is white plaque (5). In colposcopic terminology, this plaque is white epithelium visible before application of acetic acid. Leukoplakia is caused by a layer of keratin on the surface of the epithelium. Immature squamous epithelial cells have the potential to develop into keratin-producing cells or glycogen-producing cells. In the vagina and on the cervix, the normal differentiation is toward glycogen. Keratin production is abnormal in the cervicovaginal mucosa. Leukoplakia can be caused by HPV; keratinizing CIN; keratinizing carcinoma; chronic trauma from diaphragm, pessary, or tampon use; and radiotherapy.

Leukoplakia should not be confused with the white plaque of a monilial infection, which can be completely wiped off with a cotton-tipped applicator. Currently, the most common reason for leukoplakia is HPV infection (Fig. 17.8). Because it is not possible to see through the thick keratin layer to the underlying vasculature during colposcopy, such areas should undergo biopsy to rule out keratinizing carcinoma.

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Figure 17.8 Colposcopy of cervical intraepithelial neoplasia 2 associated with human papillomavirus infection of the cervix.

Punctation Dilated capillaries terminating on the surface appear from the ends as a collection of dots and thus are referred to as punctation (Fig. 17.9). When these vessels occur in a well-demarcated area of acetowhite epithelium, they indicate an

abnormal epithelium—most often CIN (5) (Fig. 17.10). The punctate vessels are formed as the metaplastic epithelium migrates over the columnar villi. Normally, the capillary regresses; however, when CIN occurs, the capillary persists and appears more prominent.

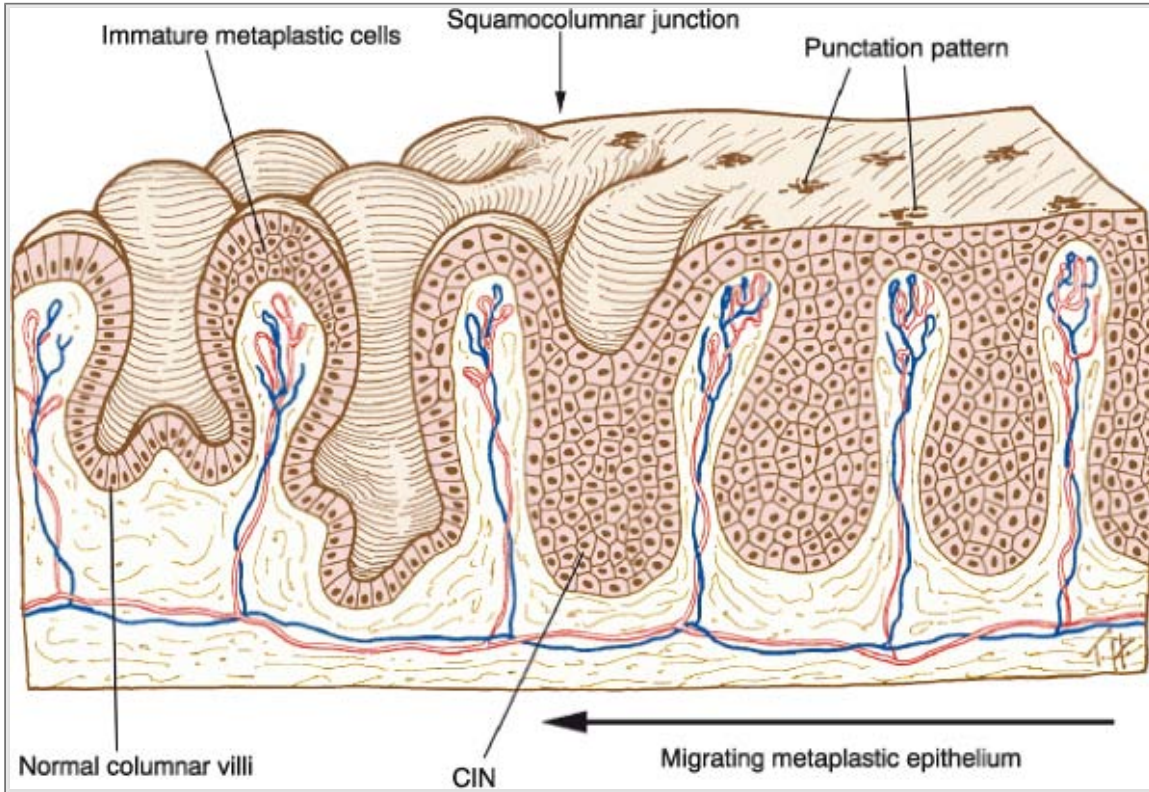


Figure 17.9 Diagram of punctation. The central capillaries of the columnar villi are preserved and produce the punctate vessels on the surface.



Figure 17.10 Human papillomavirus/cervical intraepithelial neoplasia 2 presents as a white lesion with surface spicules.

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Mosaic Terminal capillaries surrounding roughly circular or polygonal-shaped blocks of acetowhite epithelium crowded together are called mosaic because their appearance is similar to mosaic tile (Fig. 17.11). These vessels form a "basket" around the blocks of abnormal epithelium. They may arise from a coalescence of many terminal punctate vessels or from the vessels that surround the cervical gland openings (5). Mosaicism tends to be associated with higher-grade lesions and CIN 2 (Fig 17.12) and CIN 3 (Fig. 17.13).

Atypical Vascular Pattern Atypical vascular patterns are characteristic of invasive cervical cancer and include looped vessels, branching vessels, and reticular vessels. These patterns are discussed in Chapter 34.

Endocervical Curettage ASCCP guidelines do not require endocervical curettage. In cases when an endocervical sample is needed, a cytobrush is sufficient for sampling the endocervical canal.

Cervical Biopsy The cervical biopsy is performed at the area most likely to have dysplasia. If the lesion is large or multifocal, multiple biopsies may be necessary to be assured of a complete sample of the affected tissue.

Correlation of Findings

Ideally, both the pathologist and colposcopist should review the colposcopic findings and the results of cytologic assessment, cervical biopsy, and endocervical sample before deciding therapy. This is particularly true when operators are first learning the technique of colposcopy. The cytology results should not be sent to one laboratory and the histology results to another. The colposcopist should not treat the report but rather treat the disease. When the cytology and biopsy results correlate, the colposcopist can be reasonably certain that the worst lesion has been identified. If the cytology indicates a more significant lesion than the histology, the patient should undergo further evaluation, and additional biopsies as necessary. An algorithm for the evaluation, treatment, and follow-up of abnormal Pap test results is presented in Fig. 17.14.

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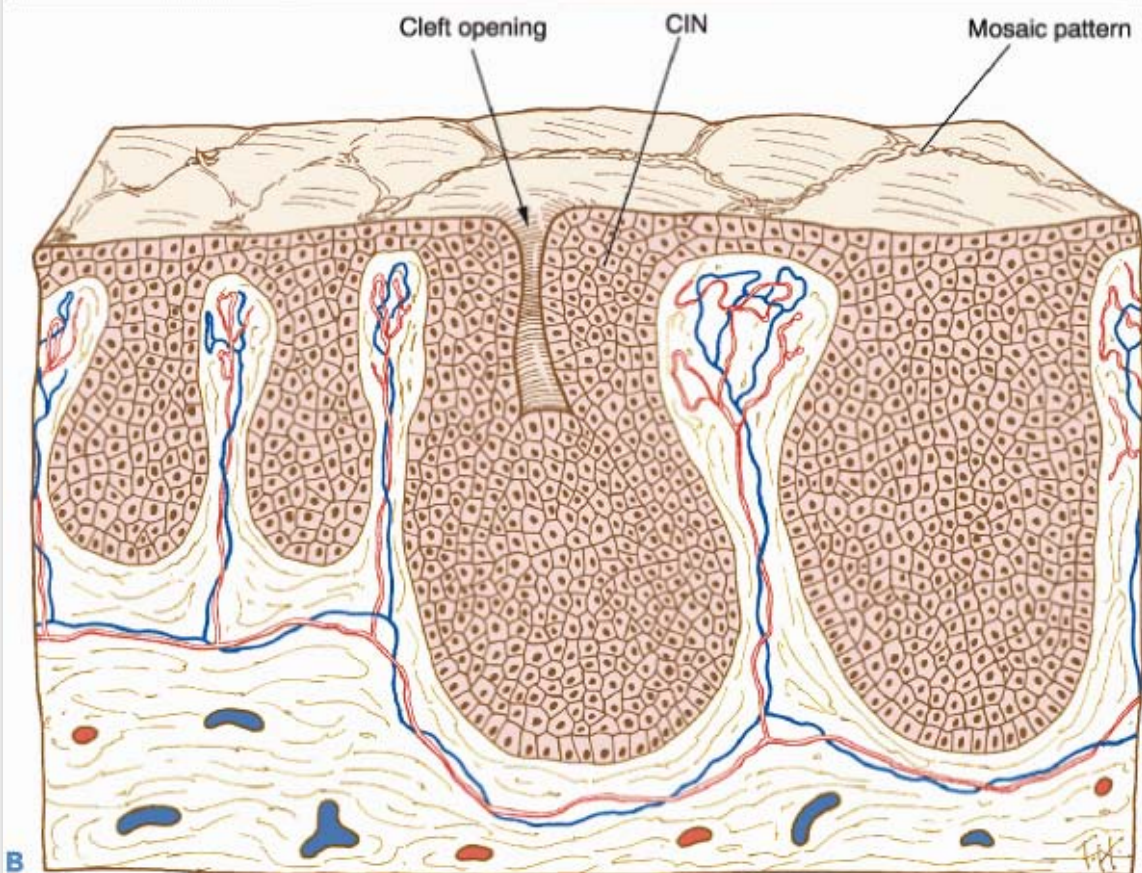


Figure 17.11 (A) Mosaic pattern and punctuation. This pattern develops as islands of dysplastic epithelium proliferate and push the ends of the superficial blood vessels away, creating a pattern that looks like mosaic tiles. **(B) Diagram of mosaic pattern.**

Histologic Terminology

CIN 1

The spontaneous regression rate of biopsy-proven CIN 1 is 60% to 85% in prospective studies. The regressions typically occur within a 2-year follow-up with cytology and colposcopy (4,68,69,70,71). **This information has led to the recommendation that patients who have biopsy diagnoses of CIN 1 with satisfactory colposcopy and who agree to**

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the evaluation every 6 months may be treated by observation with Pap testing performed at 6 and 12 months or HPV DNA testing at 12 months. After two negative test results or a single negative HPV DNA test, annual screening may be resumed. Colposcopy and repeat cytology at 12 months is another acceptable alternative (68). If the lesions progress during follow-up or persist at 2 years, ablative treatment should be performed. Regression of CIN 1 decreases after 24 months, with the regression rate becoming the same as for CIN 2 by 5 years (72).



Figure 17.12 Human papillomavirus/cervical intraepithelial neoplasia 3. Cribriform pattern of HPV at periphery with mosaicism and punctation near the squamocolumnar junction.

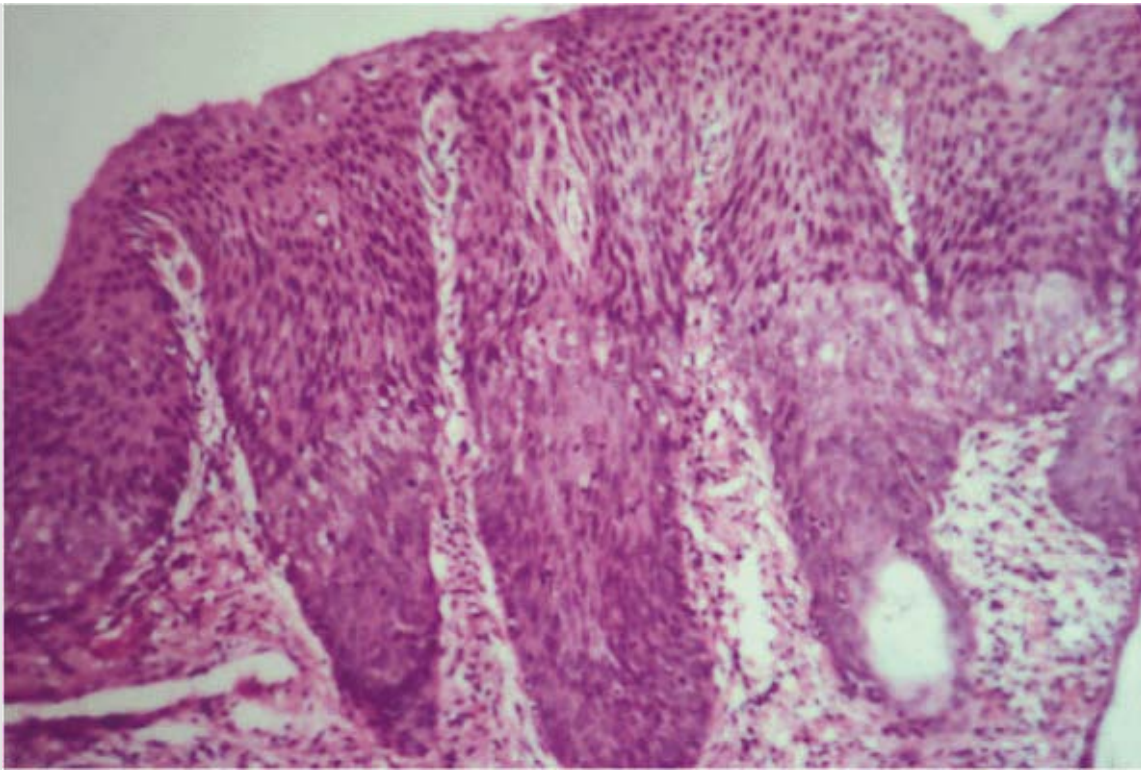


Figure 17.13 Cervical intraepithelial neoplasia grade 3.

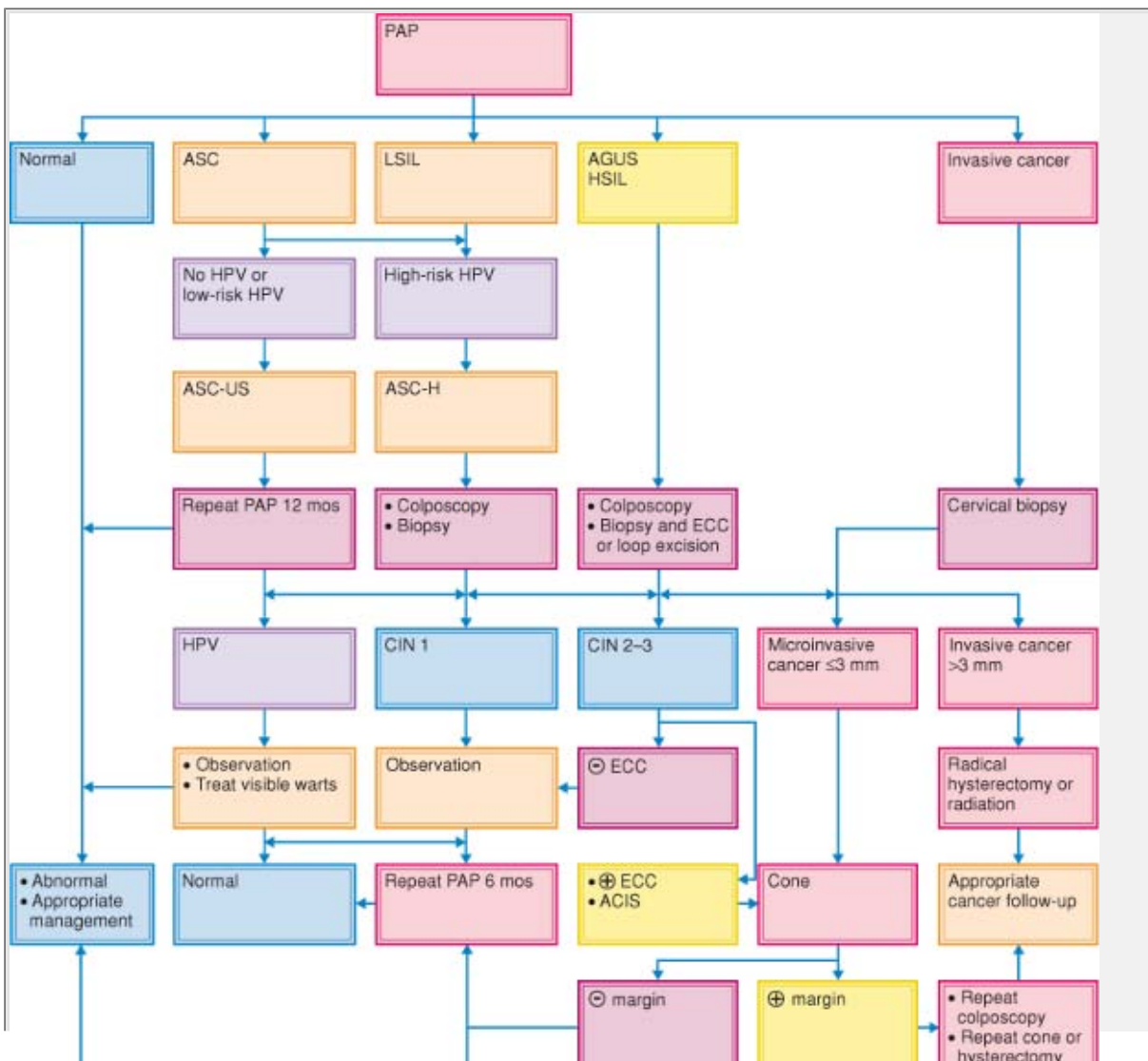




Figure 17.14 An algorithm for the evaluation, treatment, and follow-up of an abnormal Papanicolaou test.

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For patients with persistent CIN 1 after 24 months, the choice of treatment is optional. Expectant management is still acceptable, as long as the patient is cooperative with follow up. Patients with chronic systemic disease associated with immunosuppression, such as those requiring steroids or antirejection drugs, may have chronically persistent low-grade abnormalities. Ablative therapies, including cryotherapy or laser ablation, seem preferable to excisional procedures including loop electrosurgical excision procedure (LEEP) (62). A randomized prospective trial comparing cryosurgery with laser and LEEP showed no difference in persistent disease rate (4%) or recurrent disease rate (17%). Cryosurgery has the advantage of low cost and ease of use. The disadvantages are lack of tissue specimen, inability to adapt to lesion size, and posttreatment vaginal discharge. If colposcopy findings are unsatisfactory, an endocervical biopsy is imperative

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to exclude an occult high-grade lesion, which could be present in up to 10% of cases when the squamocolumnar lesion is not visualized.

CIN 2 and 3

All CIN 2 and 3 lesions require treatment. This recommendation is based on a metaanalysis showing that CIN 2 progresses to CIS in 20% of cases and to invasion in 5%. Progression of CIS to invasion is 5% (73).

Although CIN can be treated with a variety of techniques, the preferred treatment for CIN 2 and 3 has become LEEP. These techniques allow a specimen to be sent for evaluation and enable the pathologist to identify occult microinvasive cancer or adenomatous lesions to ensure these lesions have been treated adequately. The persistent and recurrent disease rates are 4% to 10% (74,75).

Treatment of CIN

Most of the ablative techniques used to treat CIN can be performed in an outpatient setting, which is one of the main objectives in the management of this disease. Because all therapeutic modalities carry an inherent recurrence rate of up to 10%, cytologic follow-up at about 3-month intervals for 1 year is necessary. Ablative therapy is appropriate when the following conditions exist:

- There is no evidence of microinvasive or invasive cancer on cytology, colposcopy, endocervical curettage, or biopsy.
- The lesion is located on the ectocervix and can be seen entirely.
- There is no involvement of the endocervix with high-grade dysplasia as determined by colposcopy and endocervical curettage.

Cryotherapy

Cryotherapy destroys the surface epithelium of the cervix by crystallizing the intracellular water, resulting in the eventual destruction of the cell. The temperature needed for effective destruction must be in the range of (-20° to -30°C). Nitrous oxide (-89°C) and carbon dioxide (-65°C) produce temperatures below this range and, therefore, are the most commonly used gases for this procedure.

The technique believed to be most effective is a freeze-thaw-freeze method in which an ice ball is achieved 5 mm beyond the edge of the probe. The time required for this process is related to the pressure of the gas; the higher the pressure, the faster the ice ball is achieved. Cryotherapy has been shown to be an effective method of treatment for CIN with very acceptable failure rates under certain conditions (76,77,78,79). It is a relatively safe procedure with few complications. Cervical stenosis is rare but can occur. Posttreatment bleeding is uncommon and is usually related to infection.

Cure rates are related to the grade of the lesion; CIN 3 has a greater chance of treatment failure (Table 17.4). Townsend has shown that cures are also related to the size of the lesion; those covering most of the ectocervix have failure rates as high as 42%, compared with a 7% failure rate for lesions less than 1 cm in diameter (80). Positive findings on endocervical curettage also can reduce the cure rate significantly. Endocervical gland involvement is important because the failure rate in women with gland involvement was 27%, compared with 9% in those who did not have such involvement (81).

Cryotherapy should be considered acceptable therapy when the following criteria are met:

- Cervical intraepithelial neoplasia, grade 1 to 2
- Small lesion
- Ectocervical location only
- Negative endocervical sample
- No endocervical gland involvement on biopsy

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**Table 17.4 Results of Cryotherapy for Cervical Intraepithelial Neoplasia (CIN)
Compared with Grade of CIN**

Author (ref. no.)	CIN 1		CIN 2		CIN 3	
	No.	Failure (%)	No.	Failure (%)	No.	Failure (%)
Ostergard (77)	13/205	6.3	7/93	7.5	9/46	19.6
Creasman et al.(78)	15/276	5.4	17/235	7.2	46/259	17.8
Benedet et al.(79)	7/143	4.9	19/448	4.2	65/1,003	6.5
Anderson and Hartley (81)			9/123	7.3	17/74	23.0
Total	35/624	5.6	50/899	5.6	137/1,382	9.9

Laser Ablation

Laser ablation has been used effectively for the treatment of CIN (Table 17.5). However, because of the expense of the equipment as well as necessity for special training, laser ablation has fallen out of favor. Additionally, because much early CIN is being managed conservatively, the need for any kind of ablation is decreasing.

Loop Electrosurgical Excision

Laser electrosurgical excision is a valuable tool for the diagnosis and treatment of CIN (82,83,84,85,86,87,88,89,90,91,92). It offers the advantage of performing a operation that is simultaneously diagnostic and therapeutic during one outpatient visit (93,94,95,96,97,98,99,100,101,102,103,104).

The tissue effect of electricity depends on the concentration of electrons (size of the wire), the power (watts), and the water content of the tissue. If low power or a large-diameter wire is used, the effect will be electrocautery, and the thermal damage to tissue will be extensive. If the power is high (35–55 watts) and the wire loop is small (0.5 mm), the effect will be electrosurgical, and the tissue will have little thermal damage. The actual cutting is a result of a steam envelope developing at the interface between the wire loop and the water-laden tissue. This envelope is then pushed through the tissue, and the combination of electron flow and acoustical events separates the tissue. After the excision, a 5-mm diameter ball electrode is used, and the power is set at 50 watts. The ball is placed near the surface so that a spark occurs between the ball and the tissue. This process is called *electrofulguration*, and it results in some thermal damage that

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leads to hemostasis. If too much fulguration occurs, the patient will develop an eschar with more discharge, and the risk for infection and late bleeding will be higher.

Table 17.5 Success Rate for Laser Vaporization

Author (ref. no.)	CIN 1		CIN 2		CIN 3	
	No.	NED (%)	No.	NED (%)	No.	NED (%)
Burke (93)	49	41 (83.6)	42	36 (85.7)	40	31 (77.5)
Wright et al. (94)	110	108 (98.2)	140	133 (95)	190	179 (94.2)
Rylander et al. (95)	22	21 (95.5)	49	48 (97.9)	133	116 (87.2)
Jordan et al. (96)	142	140 (98.6)	153	145 (94.7)	416	390 (93.8)
Benedet et al. (98)	312	301 (96.5)	472	428 (90.7)	773	702 (90.8)
Baggish et al. (101)	741	675 (91.1)	1,048	978 (93.3)	1,281	1,228 (96)
Total	1,376	1,286 (93.5)	1,904	1,768 (92.9)	2,833	2,646 (93.4)

NED = No evidence of disease.

Table 17.6 Therapeutic Efficiency of Cervical Conization: Comparison between Laser and Knife Techniques

Percentage of patients who are "cured" by conization

Author (ref. no.)	Laser (%)	Author (ref. no.)	Knife (%)
Wright et al. (94)	96.2	Larsson et al. (99)	94.0
Baggish et al. (97)	97.5	Bostofte et al. (100)	90.2
Larsson et al. (99)	95.6	Bjerre et al. ^a (102)	94.8
Bostofte et al. (100)	93.2	Kolstad et al. ^a (103)	97.6

^aPatients had negative cone margins.

Recent research has shown that LEEP is associated with an increased risk of overall preterm delivery, preterm delivery after premature rupture of membranes, and low-birthweight infants in subsequent pregnancies at greater than 20 weeks gestation (105).

Loop excision should not be used before an intraepithelial lesion that requires treatment has been identified. The risk of the "see and treat" philosophy is that in women with only metaplasia, the entire transformation zone will be removed along with varying amounts of the cervical canal, thus potentially compromising fertility (90,92). This is particularly true of young women, who may have large, immature transformation zones with extensive acetowhite areas. Complications following loop electrosurgical excision are fairly minimal and compare favorably with those following laser ablation and conization. Intraoperative hemorrhage, postoperative hemorrhage, and cervical stenosis can occur but at acceptably low rates, as noted in Table 17.6. The SCJ is visible in more than 90% of patients after this procedure. Effectiveness of LEEP and comparison of LEEP to other excision procedures are shown in Tables 17.7, 17.8 through 17.9.

Conization

Conization of the cervix plays an important role in the management of CIN. Before the availability of colposcopy, conization was the standard method of evaluating an abnormal Pap test result. **Conization is both a diagnostic and therapeutic procedure and has the advantage over ablative therapies of providing tissue for further evaluation to rule out invasive cancer (97,99,102,104,106).**

Conization is indicated for diagnosis in women with HSIL based on a Pap test under the following conditions:

- Limits of the lesion cannot be visualized with colposcopy.
- The SCJ is not seen at colposcopy.
- Endocervical curettage (ECC) histologic findings are positive for CIN 2 or CIN 3.
- There is a substantial lack of correlation between cytology, biopsy, and colposcopy results.
- Microinvasion is suspected based on biopsy, colposcopy, or cytology results.
- The colposcopist is unable to rule out invasive cancer.

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Table 17.7 Perioperative and Postoperative Bleeding From Cervical Conization: Comparison between Laser and Knife Techniques

<i>Percentage of patients undergoing conization who develop significant vaginal bleeding</i>			
<i>Author (ref. no.)</i>	<i>Laser (%)</i>	<i>Author (ref. no.)</i>	<i>Knife (%)</i>
Wright et al. (94)	12.2	Larsson et al. (99)	14.8
Baggish(97)	2.5	Bostofte et al. (100)	17.0
Larsson et al. (99)	2.3	Jones (104)	10.0
Bostofte (100)	5.0	Luesley et al. (106)	13.0

Table 17.8 Complications of Electrosurgical Excision

<i>Complications</i>	<i>No. of Patients</i>	<i>Operative Hemorrhage</i>	<i>Postoperative Hemorrhage</i>	<i>Cervical Stenosis</i>
Prendiville et al. (82)	111	2	2	—
Whiteley et al. (83)	80	0	3	—
Mor-Yosef et al. (84)	50	1	3	—
Bigrigg et al. (85)	1,000	0	6	—
Gunasekera et al. (86)	98	0	0	—
Howe et al. (87)	100	0	1	—
Minucci et al. (88)	130	0	1	2
Wright et al. (89)	432	0	8	2
Luesley et al. (90)	616	0	24	7
TOTAL	2,617	3 (0.001%)	48 (1.8%)	11/6178 (1.0%)

Lesions with positive margins are more likely to recur after conization (97,99,102) (Table 17.10). Endocervical gland involvement also is predictive of recurrence (23.6% with gland involvement compared with 11.3% without gland involvement) (107). When compared with conization, LEEP is the simpler technique, and short-term results are similar to those obtained with conization or laser excision (74,108). In a prospective study examining the long-term effects of LEEP, conization, and laser excision, no difference in recurrence of dysplasia or in pregnancy outcomes was found (109) (Table 17.11,17.12).

Hysterectomy

Hysterectomy is currently considered too radical for treatment of CIN. In a study of 38 cases of invasive cancer occurring after hysterectomy among 8,998 women (0.4%), the

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incidence of significant bleeding, infection, and other complications, including death, is higher with hysterectomy than with other means of treating CIN (110). There are some situations in which hysterectomy remains a valid and appropriate (although mandatory) method of treatment for CIN:

<i>Author (ref. no.)</i>	<i>Patients</i>	<i>Microinvasive</i>	<i>Invasive</i>
Prendiville et al. (82)	102	1	—
Bigrigg et al. (85)	1,000	5	—
Gunasekera et al. (86)	98	—	1
Howe et al. (87)	100	1	—
Wright et al. (89)	141	3	—
Luesley et al. (90)	616	1	—
Chappatte et al. (92)	100	4	6 (adenocarcinoma <i>in situ</i>)
TOTAL	2,157	15 (0.7%)	1 (0.04%)

<i>Side Effect</i>	<i>Loop Excision (n = 98)</i>	<i>Laser (n = 101)</i>
Not unpleasant	80 (92%)	32 (32%)
Moderately unpleasant	16 (16%)	50 (50%)
Very unpleasant	2 (2%)	19 (18%)
Operative time	20–50 sec (mean, 16 sec)	4–15 min (mean, 6.5 min)

From **Gunasekera PC, Phipps JH, Lewis BV**. Large loop excision of the transformation zone (LLETZ) compared to carbon dioxide laser in the treatment of CIN: a superior mode of treatment. *Br J Obstet Gynaecol* 1990;97:995–998, with permission (86).

•
Microinvasion

- CIN 3 at limits of conization specimen in selected patients
- Poor compliance with follow-up
- Other gynecologic problems requiring hysterectomy, such as fibroids, prolapse, endometriosis, and pelvic inflammatory disease

Glandular Cell Abnormalities

Atypical Glandular Cells

The Bethesda System update in 2001 eliminates the category *atypical glandular cells of undetermined significance* (AGUS). The term should now be *atypical glandular cells* (AGC). This classification is divided into *favor neoplasia* and *not otherwise specified* (NOS). The NOS group is further divided into endocervical or endometrial origin. Also included in the glandular cell category is endocervical carcinoma *in situ* and adenocarcinoma. **Atypical endocervical cells are important because of their risk for significant disease.** In a series of 63 patients from whom subsequent cervical biopsy or hysterectomy specimens were evaluated, 17 women had CIN 2 or CIN 3, 5 women had adenocarcinoma

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in situ, and two women had invasive adenocarcinoma (107). An additional eight patients had CIN 1, and 2 women had endometrial hyperplasia. Overall, 32 patients (50.8%) had significant cervical lesions. This is a much higher positive rate than that for ASC-US Pap test results.

Table 17.11 Results of Loop Electrosurgical Excision

<i>Author (ref. no.)</i>	<i>Patients Treated</i>	<i>Patients Recurred</i>
Prendiville et al. (82)	102	2
Whiteley et al. (83)	80	4
Bigrigg et al. (85)	1,000	41
Gunasekera et al. (86)	98	7
Luesley et al. (90)	616	27
Murdoch et al. (91)	600	16
TOTAL	2,496	97 (3.9%)

Table 17.12 Recurrence of Cervical Intraepithelial Neoplasia After Cone Biopsy

<i>Author (ref. no.)</i>	<i>No. of Patients</i>	<i>Negative Margins</i>	<i>Positive Margins</i>
Larsson et al. (99)	683	56	246
Bjerre et al. (102)	1,226	64	429
Kolstad et al. (103)	1,121	27	291
TOTAL	3,030	147 (4.9%)	966 (31.9%)

Adenocarcinoma

In adenocarcinoma *in situ* (AIS), the endocervical glandular cells are replaced by tall columnar cells with nuclear stratification, hyperchromasia, irregularity, and increased mitotic activity (112). Cellular proliferation results in crowded, cribriform glands. However, the normal branching pattern of the endocervical glands is maintained. Most neoplastic cells resemble those of the endocervical mucinous epithelium. Endometrioid and intestinal cell types occur less often. About 50% of women with cervical AIS also have squamous CIN. Thus, some of the AIS lesions represent incidental findings in specimens removed for treatment of squamous neoplasia. **Because AIS is located near or above the transformation zone, conventional cervical specimens may not be effective for detecting AIS.**

Obtaining specimens by cytobrush may improve detection of AIS. If the focus of AIS is small, cervical biopsy and endocervical curettage may have negative findings. In such cases, a more comprehensive survey of the cervix by conization is necessary. This type of specimen also allows exclusion of coexisting invasive adenocarcinoma. **The term *microinvasion* should not be used to describe adenocarcinomas.** Once the gland has been invaded, there is no definable technique for identifying the true "depth of invasion" because the invasion may have originated from the mucosal surface or the periphery of the underlying glands. The "breakthrough" of the basement membrane cannot truly be described; therefore, the tumor is either AIS or invasive adenocarcinoma.

With the recent apparent increase in invasive adenocarcinoma of the endocervix, more attention has been directed toward AIS. There is evidence that AIS may progress to invasive cancer (84). In a series of 52 cases of adenocarcinoma of the uterine cervix, the results of 18 endocervical biopsies were interpreted as negative 3 to 7 years before the presentation with cancer (112). In five of these cases, AIS was found.

In a study of the anatomic distribution of AIS in 23 women (113), all patients had AIS involving both the surface and the glandular endocervical epithelium, often with the deepest glandular cleft also involved. The entire endocervical canal was at risk; nearly one half of the patients had lesions 1.5 to 3 cm from the external os. Overall, 15 patients had unifocal disease, 3 had multifocal disease, and 5 had AIS of undermined type; 11 of the 23 patients had squamous intraepithelial lesions as well as AIS. In a study of 40 patients with AIS who had cervical conization (110), 23 of 40 patients (58%) had coexisting squamous intraepithelial lesions, and 2 had invasive squamous cell carcinoma. Of the 22 patients who underwent hysterectomy, the margins on the cone specimen were positive in 10 patients, and 70% had residual AIS, including 2 patients with foci of invasive adenocarcinoma. One of the 12 patients with negative margins had focal residual adenocarcinoma in the hysterectomy specimen, and 18 women had conization only with negative margins and no

relapse of disease after a medium interval of 3 years. Thus, positive margins on the conization specimen are significant findings in these patients.

In a more alarming study of 28 patients with AIS (115), of the 8 patients with positive margins who underwent repeat conization or hysterectomy, 3 had residual AIS, and 1 patient had invasive adenocarcinoma. Of 10 patients with negative margins who underwent hysterectomy or repeat conization, 4 had residual AIS. One patient in whom the cone margin could not be evaluated was found to have invasive adenocarcinoma. Of the 15 patients treated conservatively with repeat conization of the cervix and close follow-up, 7 (47%) had a recurrent glandular lesion detected after the conization, including invasive adenocarcinoma in 2 women. More disturbing is the finding that a glandular lesion was not suspected in 48% of the patients, based on Pap test and endocervical curettage results obtained before conization of the cervix.

AIS must be considered a serious cancer precursor of adenocarcinoma. The entire endocervical canal is at risk, and detection of the lesion with cytologic assessment or endocervical curettage may not be reliable. Any patient with a positive cone margin should undergo repeat conization. If fertility is not desired, a hysterectomy should be performed because of the risk of recurrence, even in the presence of negative margins.

Vaginal Intraepithelial Neoplasia

Vaginal intraepithelial neoplasia (VAIN) often accompanies CIN and is believed to have a similar cause (116). Such lesions may be extensions onto the vagina from the CIN, or they may be satellite lesions occurring mainly in the upper vagina. **Because the vagina does not have a transformation zone with immature epithelial cells to be infected by HPV, the mechanism of entry of HPV is by way of skin abrasions from coitus or tampon use.** As these abrasions heal with metaplastic squamous cells, the HPV may begin its growth in a manner similar to that in the cervical transformation zone.

Signs

VAIN lesions are asymptomatic. Because they often accompany active HPV infection, the patient may report vulvar warts or an odoriferous vaginal discharge from vaginal warts.

Screening

Women with an intact cervix should undergo routine cytologic screening. **Because VAIN is nearly always accompanied by CIN, the Pap test result is likely to be positive when VAIN is present. The vagina should be carefully inspected by colposcopic examination at the time of colposcopy for any CIN lesion.** Particular attention should be paid to the upper vagina. **Women who have persistent positive Pap test results after treatment of CIN should be examined carefully for VAIN.** For women in whom the cervix has been removed for cervical neoplasia, Pap testing should be performed at regular intervals initially, depending on the diagnosis and severity of lesion, and yearly thereafter.

Diagnosis

Colposcopic examination and directed biopsy are the mainstays of diagnosis of VAIN. Typically, the lesions are located along the vaginal ridges, are ovoid in shape and slightly raised, and often have surface spicules. VAIN 1 lesions usually are accompanied by a significant amount of koilocytosis, indicating their HPV origin (Fig. 17.15). As the lesions progress to VAIN 2,

they exhibit a thicker acetowhite epithelium, a more raised external border, and less iodine uptake (Fig. 17.16A). When VAIN 3 occurs, the surface may

become papillary, and the vascular patterns of punctation and mosaic may occur (Fig. 17.16B). Early invasion is typified by vascular patterns similar to those of the cervix.



Figure 17.15 Human papillomavirus/vaginal intraepithelial neoplasia grade 1. Note the surface spicules with partial uptake of Lugol's stain.

Treatment

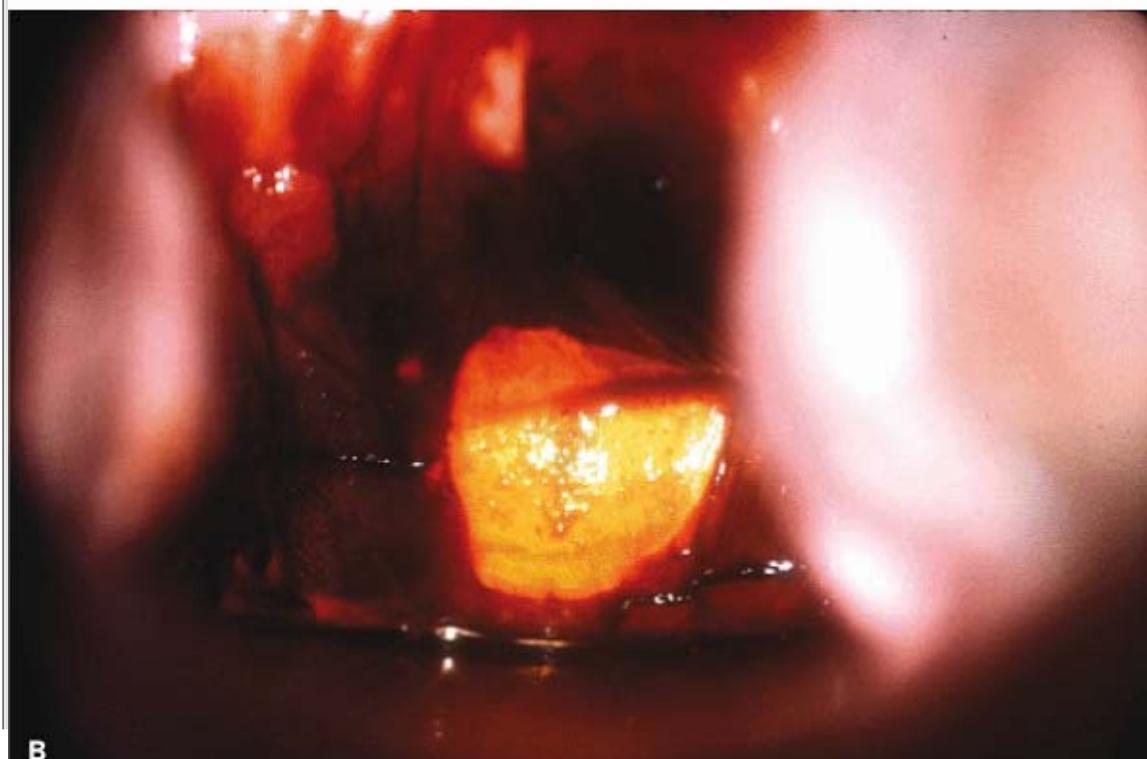
Patients with VAIN 1 and HPV infection do not require treatment. These lesions often regress, are multifocal, and recur quickly when treated with ablative therapy. VAIN 2 lesions can be managed expectantly or treated by laser ablation. VAIN 3 lesions are more likely to harbor an early invasive lesion. In a study of 32 patients who underwent upper vaginectomy for VAIN 3 (117), occult invasive carcinoma was found in 9 patients (28%). It is recommended in older patients that VAIN 3 lesions located in the dimples of the vaginal cuff be excised to rule out occult invasive cancer. **VAIN 3 lesions that are adequately sampled to rule out invasive disease can be treated with laser therapy. The major advantage of laser vaporization therapy is the ability to control exactly the depth and width of destruction by direct vision through the colposcope.** The other major advantage of laser therapy is the rapid posttreatment healing phase. This process takes about 3 to 4 weeks, after which time a new epithelium has formed completely and, in most cases, has a mature glycogen-containing epithelium.

Tissue Interaction When the laser beam contacts tissue, its energy is absorbed by the water in the cells, causing it to boil instantly. The cells explode into a puff of vapor (thus the term *laser vaporization*). The protein and mineral content is incinerated by the heat and leaves a charred appearance at the base of the exposed area. The depth of laser destruction is a function of the power of the beam (in watts), the area of the beam (in millimeters squared), and the

length of time the laser remains in the tissue. The beam must be moved uniformly across the tissue surface to prevent deep destruction. The laser beam vaporizes a central area and leaves a narrow zone of heat necrosis surrounding the laser crater. The goal of laser vaporization is to minimize this area of tissue necrosis. This goal is accomplished by using high wattage (20 watts) with medium beam size (1.5 mm) and moving the beam uniformly but quickly over the surface. The zone of thermal necrosis will be 0.1 mm when the laser is used in this manner. Some lasers have a function

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called *super pulse*, in which the laser beam is electronically switched off and on thousands of times per second, thereby allowing the tissue to cool between pulses to create less thermal necrosis.



B

Figure 17.16 (A) Vaginal intraepithelial neoplasia grade 2. (B) Vaginal intraepithelial neoplasia grade 3.

Cryosurgery should not be used in the vagina because the depth of injury cannot be controlled and inadvertent injury to the bladder or rectum may occur.

Superficial fulguration with electrosurgical ball cautery may be used under colposcopic control to observe the depth of destruction by wiping away the epithelial tissue as it is ablated. Excision is an excellent method for treatment of upper vaginal lesions in a small area. Occasionally, total vaginectomy will be required for a VAIN 3 lesion occupying the entire

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vagina. It should be accompanied by a split-thickness skin graft. This aggressive treatment for widespread vaginal lesions should not be used for VAIN 2.

The malignant potential of VAIN appears to be less than that of CIN. In a review of 136 cases of CIS of the vagina over a 30-year period (116), 4 cases (3%) progressed to invasive vaginal cancer despite the use of various treatment methods.

Vulvar Intraepithelial Disease

Vulvar Dysmorphies

In the past, terms such as *leukoplakia*, *lichen sclerosus et atrophicus*, *primary atrophy*, *sclerotic dermatosis*, *atrophic and hyperplastic vulvitis*, and *kraurosis vulvae* have been used to denote disorders of epithelial growth and differentiation (118). In 1966, Jeffcoate (119) suggested that these terms did not refer to separate disease entities because their macroscopic and microscopic appearances were variable and interchangeable. He assigned the generic term *chronic vulvar dystrophy* to the entire group of lesions.

The International Society for the Study of Vulvar Disease (ISSVD) recommended that the old *dystrophy* terminology be replaced by a new classification under the pathologic heading *nonneoplastic epithelial disorders of skin and mucosa*. This classification is shown in Table 17.13. In all cases, diagnosis requires biopsy of suspicious-looking lesions, which are best detected by careful inspection of the vulva in a bright light aided, if necessary, by a magnifying glass (120).

The malignant potential of these nonneoplastic epithelial disorders is low, particularly now that the lesions with atypia are classified as vulvar intraepithelial neoplasia (VIN). However, patients with lichen sclerosus and concomitant hyperplasia may be at particular risk (121).

Vulvar Intraepithelial

As with the vulvar dysmorphies, there has been confusion regarding the nomenclature for **Neoplasia** VIN. Four major terms have been used: *erythroplasia of Queyrat*, *Bowen's disease*, *carcinoma in situ simplex*, and *Paget's disease*. In 1976, the ISSVD decreed that the first three

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lesions were merely gross variants of the same disease process and that all of these entities should be included under the umbrella term *squamous cell carcinoma in situ* (stage 0) (90). In 1986, the ISSVD recommended the term *vulvar intraepithelial neoplasia* (Table 17.13).

Table 17.13 Classification of Epithelial Vulvar Diseases

Nonneoplastic epithelial disorders of skin and mucosa

Lichen sclerosis (lichen sclerosis et atrophicus)
 Squamous hyperplasia (formerly hyperplastic dystrophy)
 Other dermatoses

Mixed nonneoplastic and neoplastic epithelial disorders**Intraepithelial neoplasia**

Squamous intraepithelial neoplasia
 VIN 1
 VIN 2
 VIN 3 (severe dysplasia or carcinoma *in situ*)
 Nonsquamous intraepithelial neoplasia
 Paget's disease
 Tumors of melanocytes, noninvasive

Invasive tumors

VIN, vulvar intraepithelial neoplasia.

From **Committee on Terminology, International Society for the Study of Vulvar Disease**. New

nomenclature for vulvar disease. *Int J Gynecol Pathol* 1989;8:83, with permission (120).



Figure 17.17 Carcinoma *in situ* of the vulva (vulvar intraepithelial neoplasia grade 3).

VIN is graded as 1 (mild dysplasia), 2 (moderate dysplasia), or 3 (severe dysplasia or CIS) on the basis of cellular immaturity, nuclear abnormalities, maturation disturbance, and mitotic activity. In VIN 1, immature cells, cellular disorganization, and mitotic activity occur predominantly in the lower one third of the epithelium, whereas in VIN 3, immature cells with scanty cytoplasm and severe chromatinic alterations occupy most of the epithelium

(Fig. 17.17). Dyskeratotic cells and mitotic figures occur in the superficial layer. The appearance of VIN 2 is intermediate between VIN 1 and VIN 3. Additional cytopathic changes of HPV infection, such as perinuclear halos with displacement of the nuclei by the intracytoplasmic viral protein, thickened cell borders, binucleation, and multinucleation, are common in the superficial layers of VIN, especially in VIN 1 and VIN 2. These viral changes are not definitive evidence of neoplasia but are indicative of viral exposure (122). Most vulvar condylomas are associated with HPV-6 and -11, whereas HPV-16 is detected in more than 80% of VIN cases by molecular techniques.

VIN 3 can be unifocal or multifocal. Typically, multifocal VIN 3 presents with small hyperpigmented lesions on the labia majora (Fig. 17.18). Some cases of VIN 3 are more confluent, extending to the posterior fourchette and involving the perineal tissues. The term *bowenoid papulosis* (*bowenoid dysplasia*) has been used to describe multifocal VIN lesions ranging from grade 1 to 3. Clinically, patients with bowenoid papulosis present with multiple small pigmented papules (40% of cases) that are usually less than 5 mm in diameter. Most women with these lesions are in their 20s, and some are pregnant. After childbirth, the lesions may regress spontaneously. However, the term *bowenoid papulosis* is no longer recommended by the ISSVD.

Paget's Disease of the Vulva

Extramammary Paget's disease of the vulva (AIS) was described 27 years after the description by Sir James Paget of the mammary lesion that now bears his name (123).

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Some patients with vulvar Paget's disease have an underlying adenocarcinoma, although the precise frequency is difficult to ascertain.

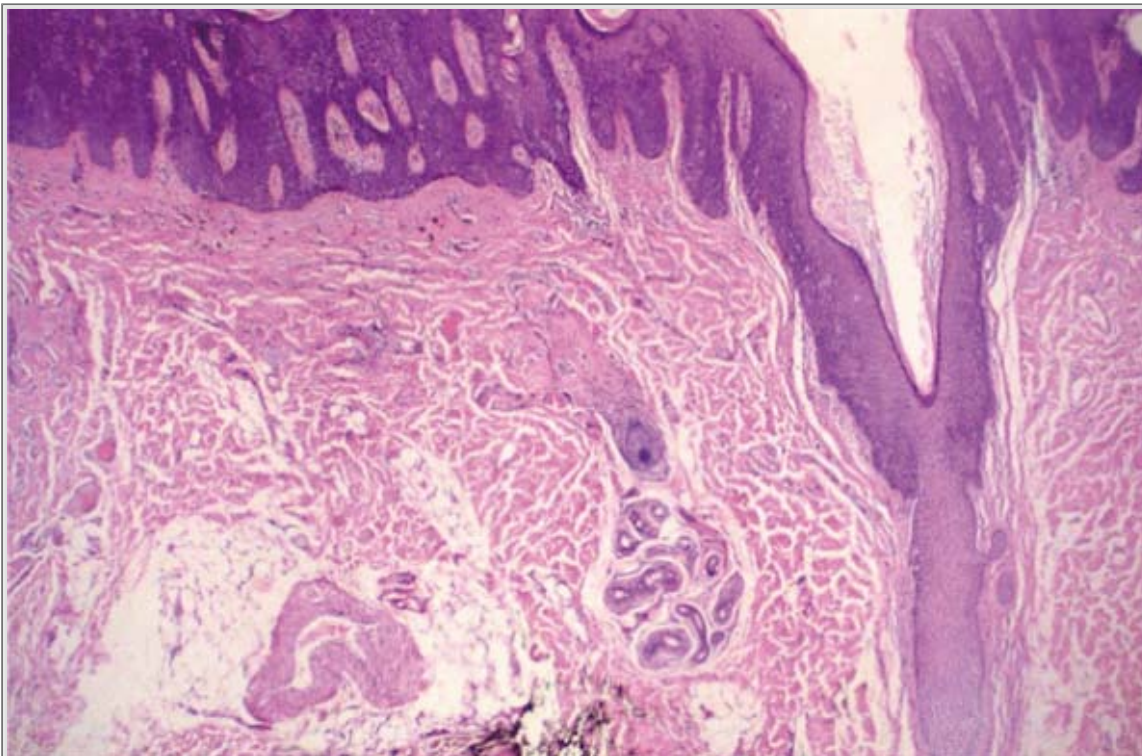


Figure 17.18 Vulvar carcinoma *in situ*: carcinoma *in situ* extending into the hair follicle.

Histology

Most cases of vulvar Paget's disease are intraepithelial. Because these lesions demonstrate apocrine differentiation, the malignant cells are believed to arise from undifferentiated basal cells, which convert into an appendage type of cell during carcinogenesis (Fig. 17.19). The "transformed cells" spread intraepithelially throughout the squamous epithelium and may extend into the appendages. In most patients with an underlying invasive carcinoma of the apocrine sweat gland, Bartholin gland, or anorectum, the malignant cells are believed to migrate through the dermal ductal structures and reach the epidermis. In such cases, metastasis to the regional lymph nodes and other sites can occur.

Paget's disease must be distinguished from superficial spreading melanoma. All sections should be studied thoroughly using differential staining, particularly periodic acid–Schiff (PAS) and mucicarmine stains. Mucicarmine has routinely positive results in the cells of Paget's disease and negative results in melanotic lesion.

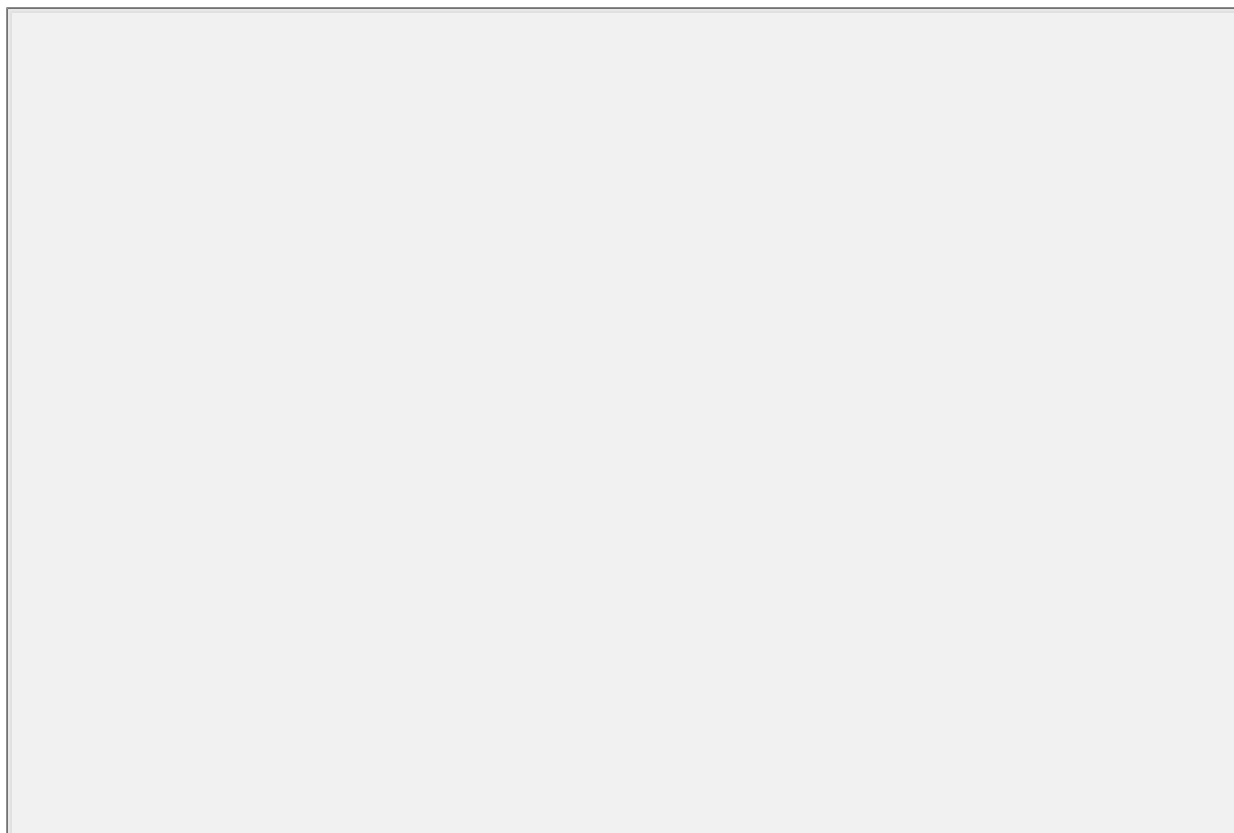
Clinical Features

Paget's disease of the vulva predominantly affects postmenopausal white women, and the presenting symptoms are usually pruritus and vulvar soreness. The lesion has an eczematoid appearance macroscopically and usually begins on the hairbearing portions of the vulva (Fig. 17.20). It may extend to involve the mons pubis, thighs, and buttocks. Extension to the mucosa of the rectum, vagina, or urinary tract also has been described (124). The more extensive lesions are usually raised and velvety in appearance.

A second synchronous or metachronous primary neoplasm is associated with extramammary Paget's disease in about 4% of patients, much less common than believed

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in the past (125). Associated carcinomas have been reported in the cervix, colon, bladder, gallbladder, and breast. When the anal mucosa is involved, there usually is an underlying rectal adenocarcinoma (121).



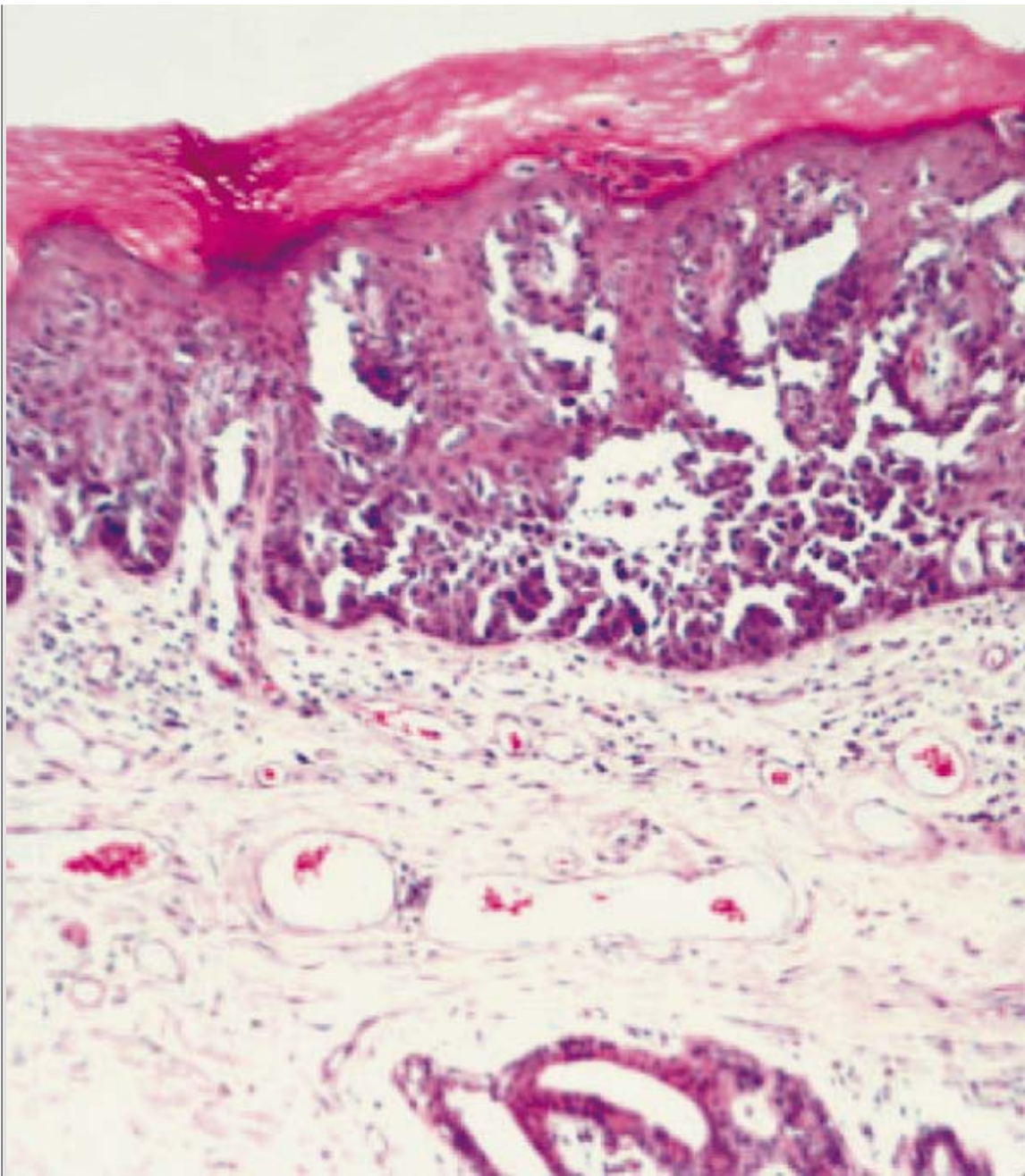


Figure 17.19 Paget's disease of vulva. The epidermis is permeated by abnormal cells with vacuolated cytoplasm and atypical nuclei. This heavy concentration of abnormal cells in the parabasal layers is typical of Paget's disease.

Treatment

VIN The treatment of VIN 3 has varied from wide excision to the performance of a superficial or "skinning" vulvectomy (126,127,128,129). Although the treatment originally recommended for CIS of the vulva was wide excision, fears that the disease frequently was preinvasive led to the widespread use of superficial vulvectomy (128). **Because progression is relatively uncommon, typically occurring in 5% to 10% of cases (126), extensive surgery is not warranted.** This is particularly true because many VIN 3 lesions are found in premenopausal women.



Figure 17.20 Paget's disease of the labium majus.

The therapeutic alternatives for VIN 3 are simple excision, laser ablation, and superficial vulvectomy with or without split-thickness skin grafting.

Excision of small foci of disease produces excellent results and has the advantage of providing a histopathologic specimen. Although multifocal or extensive lesions may be difficult to treat by this approach, it offers the potential for the most cosmetic result. Repeat excision is often necessary but can usually be accomplished without vulvectomy (127,129).

The carbon dioxide laser can be used for multifocal lesions but is unnecessary for unifocal disease. The disadvantages are that it can be painful and costly and does not provide a histopathologic specimen (130).

Superficial vulvectomy is appropriate to treat extensive and recurrent VIN 3 (129). The goal of the surgery is to extirpate all of the disease while preserving as much of the normal vulvar anatomy as possible. The anterior vulva and the clitoris should be preserved if possible. In some patients, the disease extends up the anus, which also must be resected. An effort should

be made to close the vulvar defect primarily, reserving the use of skin grafts for instances in which the vulvar defect cannot be closed because the resection is so extensive. Split-thickness skin grafts can be harvested from the thighs or buttocks, but the latter is more easily concealed (131).

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Paget's Disease Unlike squamous cell CIS, in which the histologic extent of disease usually correlates closely with the macroscopic lesion, Paget's disease usually extends well beyond the gross lesion (132). This extension results in positive surgical margins and frequent local recurrence unless a wide local excision is performed (133). **Underlying adenocarcinomas are usually apparent clinically, but this finding does not occur invariably; therefore, the underlying dermis should be removed for adequate histologic evaluation.** For this reason, laser therapy is unsatisfactory in treating primary Paget's disease. If underlying invasive carcinoma is present, it should be treated in the same manner as a squamous vulvar cancer. This treatment usually requires radical vulvectomy and at least an ipsilateral inguinal-femoral lymphadenectomy.

Recurrent lesions are almost always *in situ*, although there has been at least one report of an underlying adenocarcinoma in recurrent Paget's disease (125). In general, it is reasonable to treat recurrent lesions with surgical excision.

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Early Pregnancy Loss and Ectopic Pregnancy

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- As many as 30% of pregnancies may be spontaneously lost.
- Following an ectopic pregnancy, there is a 10-fold increase in the risk of a subsequent ectopic pregnancy.
- Single-dose *methotrexate* appears to be the treatment of choice if medical therapy is indicated and selected.
- Unless the patient has documented cardiac activity in the ectopic, medical therapy should be instituted unless all the treatment criteria are met and the patient has had at least two hCG levels and a transvaginal ultrasound.
- Surgical management and medical therapy appear to be equivalent in a randomized comparison.

An abnormal gestation can be either intrauterine or extrauterine. Extrauterine or ectopic pregnancy occurs when the fertilized ovum becomes implanted in tissue other than the endometrium. Although most ectopic gestations are located in the ampullary segment of

the fallopian tube, such pregnancies may also occur in other sites (Table 18.1).

Abnormal intrauterine pregnancy often results in pregnancy loss early in gestation. Such losses can be related to a number of factors. With both abnormal intrauterine and extrauterine gestation, early recognition is key to diagnosis and management.

Abnormal Intrauterine Pregnancy

Spontaneous Abortion

Anembryonic gestation, inevitable abortion, incomplete abortion, and completed abortion are types of first-trimester abortions. **About 15% to 20% of known pregnancies terminate in spontaneous abortion. With the use of serial human chorionic gonadotropin (hCG) measurements to detect early subclinical pregnancy losses, the percentage**

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increases to 30%. About 80% of spontaneous pregnancy losses occur in the first trimester; the incidence decreases with each gestational week. In a study of 347 patients with a first-trimester pregnancy documented by ultrasonography, the overall rate of pregnancy loss was 6.1% to 4.2% in patients without bleeding and 12.4% in patients with bleeding (1). In women who have had one prior spontaneous abortion, the rate of spontaneous abortion in a subsequent pregnancy is about 20%; in women who have had three consecutive losses, the rate is 50%. The causes of this condition are varied and most often unknown (Table 18.2). Patients should be reassured that, in most cases, spontaneous abortion does not recur.

Table 18.1 Definitions of Types of Abnormal Intrauterine and Extrauterine Pregnancies

Extrauterine Pregnancy	
Tubal pregnancy	A pregnancy occurring in the fallopian tube—most often these are located in the ampullary portion of the fallopian tube
Interstitial pregnancy	A pregnancy that implants within the interstitial portion of the fallopian tube
Abdominal pregnancy	Primary abdominal pregnancy—the first and only implantation occurs on a peritoneal surface
	Secondary abdominal pregnancy—implantation originally in the tubal ostia, subsequently aborted, and then reimplanted onto a peritoneal surface
Cervical pregnancy	Implantation of the developing conceptus in the cervical canal
Ligamentous pregnancy	A secondary form of ectopic pregnancy in which a primary tubal pregnancy erodes into the mesosalpinx and is located between the leaves of the broad ligament
Heterotopic pregnancy	A condition in which ectopic and intrauterine pregnancies coexist
Ovarian pregnancy	A condition in which an ectopic pregnancy implants within the ovarian cortex
Abnormal Intrauterine Pregnancy	
Incomplete abortion	Expulsion of some but not all of the products of conception before 20 completed weeks of gestation
Complete abortion	Spontaneous expulsion of all fetal and placental tissue from the uterine cavity before 20 weeks of gestation

Inevitable abortion	Uterine bleeding from a gestation of less than 20 weeks, accompanied by cervical dilation but without expulsion of placental or fetal tissue through the cervix
Anembryonic gestation	An intrauterine sac without fetal tissue present at more than 7.5 weeks of gestation
First-trimester fetal death	Death of the fetus in the first 12 weeks of gestation
Second-trimester fetal death	Death of the fetus between 13 and 24 weeks of gestation
Recurrent spontaneous abortion	The loss of more than three pregnancies before 20 weeks of gestation

Threatened Abortion

Threatened abortion is defined as vaginal bleeding before 20 weeks of gestation. It occurs in about 30% to 40% of all pregnancies. The bleeding is usually light and may be associated with mild lower abdominal or cramping pain. It is often not possible to differentiate clinically between threatened abortion, completed abortion, and ectopic pregnancy in an unruptured tube. The differential diagnosis in these patients includes consideration of possible cervical polyps, vaginitis, cervical carcinoma, gestational trophoblastic disease, ectopic pregnancy, trauma, and foreign body. On physical examination, the abdomen usually is not tender, and the cervix is closed. Bleeding can be seen coming from the os, and usually there is no cervical motion or adnexal tenderness. Although most patients experience bleeding at 8 to 10 weeks of gestation, the actual loss usually occurs

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before 8 weeks of gestation. Only 3.2% of patients experience a pregnancy loss after 8 weeks of gestation (2).

Table 18.2 Potential Causes of Spontaneous Pregnancy Loss

Pathologic (blighted) ovum—anembryonic gestation
Embryonic anomalies
Chromosomal anomalies
Increased maternal age
Uterine anomalies
Intrauterine device
Teratogen
Mutagen
Maternal disease
Placental anomalies
Extensive maternal trauma

Unless the patient has an intrauterine pregnancy documented by ultrasonography, eliminating the possibility of an ectopic pregnancy, evaluation of a threatened abortion should include serial measurements of hCG.

Endovaginal ultrasonography can detect a gestational sac at an hCG level of 1,000 to 2,000 mIU/mL. By 7 weeks of gestation, a fetal pole with fetal cardiac activity can be seen. When a gestational sac is visualized, subsequent loss of the pregnancy occurs in 11.5% of patients. If a yolk sac is present, the loss rate is 8.5%; with an embryo of 5 mm, the loss rate is 7.2%; with an embryo of 6 to 10 mm, the loss rate is 3.2%; and when the embryo is 10 mm, the loss rate is only 0.5%. The fetal loss rate after 14 weeks of gestation is about 2% (3). Transvaginal measurement of gestational sac size is useful in differentiating viable

from nonviable intrauterine pregnancies. A mean sac diameter greater than 13 mm without a visible yolk sac or a mean sac diameter greater than 17 mm lacking an embryo predicts nonviability in all cases (4).

There is no effective therapy for a threatened intrauterine pregnancy. Bed rest, although advocated, is not effective. Progesterone or sedatives should not be used. All patients should be counseled and reassured so that they understand the situation. Vaginal infection, if present, should be treated.

Inevitable Abortion

With an inevitable abortion, the volume of bleeding is often greater than with other types of abortion, and the cervical os is open and effaced, but no tissue has been passed. Most patients have crampy lower abdominal pain, and some have cervical motion or adnexal tenderness. When it is certain that the pregnancy is not viable because the cervical os is dilated or excessive bleeding is present, suction curettage should be performed. Blood type and Rh determination and a complete blood count should be obtained if there is any concern about the amount of bleeding. **Rh₀(D) immune globulin (RhoGAM) should be given either before or after the uterus is evacuated if the patient's blood is Rh negative.**

Incomplete Abortion

An incomplete abortion is a partial expulsion of the pregnancy tissue. Before 6 weeks of gestation, the placenta and fetus are generally passed together, but after this time, they

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often are passed separately. Although most patients have vaginal bleeding, only some have passed tissue. Lower abdominal cramping is invariably present, and the pain may be described as resembling labor. On physical examination, the cervix is dilated and effaced, and bleeding is present. Often, clots are admixed with products of conception. If the bleeding is profuse, the patient should be examined promptly for tissue protruding from the cervical os; removal of this tissue with a ring forceps reduces the bleeding. A vasovagal bradycardia may occur and responds to removal of the tissue. All patients with an incomplete abortion should undergo suction curettage as quickly as possible. A complete blood count, maternal blood type, and Rh determination should be obtained; **Rh-negative patients should receive Rh₀(D) immune globulin.**

If the patient is febrile, broad-spectrum antibiotic therapy should be administered before suction curettage is performed to reduce the incidence of postabortal endometritis and pelvic inflammatory disease, thereby reducing potential deleterious effects on fertility. The antibiotic regimen chosen should be similar to the regimens used for treatment of pelvic inflammatory disease (PID). In patients who do not have clinical signs of infection, prophylactic antibiotic therapy should be instituted. Suggested regimens include *doxycycline* (100 mg orally twice daily), *tetracycline* (250 mg orally four times daily for 5–7 days) or another antibiotic of similar spectrum.

Ectopic Gestation

Incidence

The most comprehensive data available on ectopic pregnancy rates have been collected by **the Centers for Disease Control and Prevention (5).** **These data show a significant**

increase in the number of ectopic pregnancies in the United States during the past 20 years (Fig. 18.1). In 1989, the latest year for which statistics were published, an estimated 88,400 ectopic pregnancies occurred, at a rate of 16 ectopic pregnancies per 1,000 reported pregnancies. These numbers represent a fivefold increase compared with the 1970 rates. The highest rates occurred in women aged 35 to 44 years (27.2 per 1,000 reported pregnancies). When the data are analyzed by race, the risk for ectopic pregnancy among African Americans and other minorities (20.8 per 1,000) is 1.6 times greater than the risk among whites (13.4 per 1,000). In 1988, 44 deaths were attributed to complications of ectopic pregnancy, which represents 15% of all maternal deaths. The risk for death is higher for African Americans and other minorities than for whites (6). For both races, teenagers have the highest mortality rates, but the rate for African American and other minority teenagers is almost five times that of white teenagers. **After an ectopic pregnancy, there is a 7- to 13-fold increase in the risk of a subsequent ectopic pregnancy. The chance that a subsequent pregnancy will be intrauterine is 50% to 80%, and the chance that the pregnancy will be tubal is 10% to 25%; the remaining patients will be infertile** (7,8,9). Many variables make accurate assessment of risk difficult (e.g., size and location of the ectopic pregnancy, status of the contralateral adnexa, treatment method, and history of infertility).

Etiology and Risk Factors

Tubal damage results from inflammation, infection, and surgery. Inflammation and infection may cause damage without complete tubal obstruction. Complete blockage may result from salpingitis, incomplete tubal ligation, tubal fertility surgery, partial salpingectomy, or congenital midsegment tubal atresia (10,11,12,13,14). Damage to the mucosal portion of the tube or fimbria accounts for about one half of all tubal pregnancies (15). Tubal diverticula may result in abnormalities that entrap the blastocyst or impede transport (16,17). **Tubal pregnancy may occur in a blocked tube with contralateral tubal patency, with the sperm migrating across the abdomen to fertilize an egg released from the blocked side.**

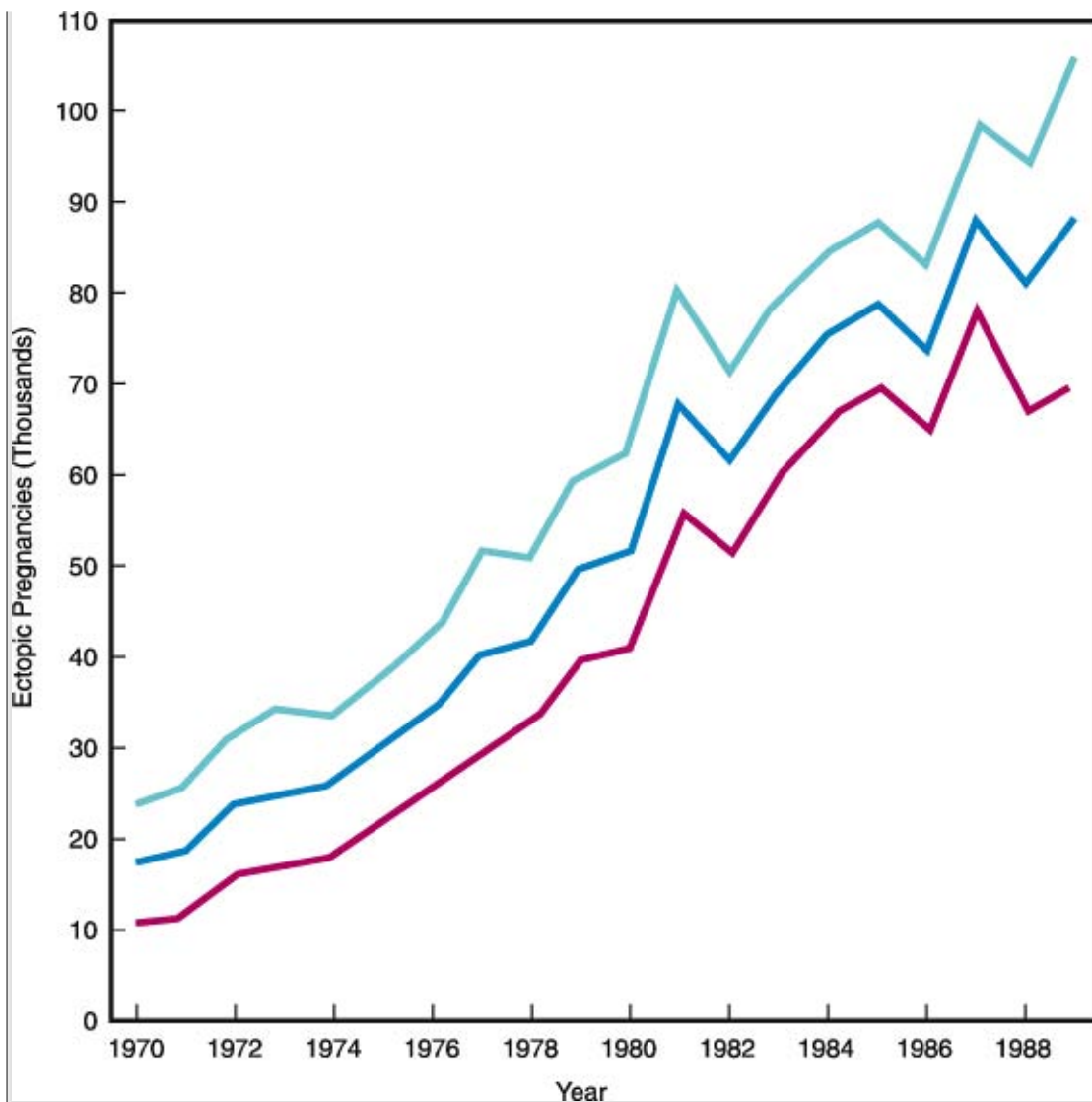


Figure 18.1 Estimation of the number of ectopic pregnancies (United States, 1970–1989). *Dashed lines* represent the upper and lower limits of 95% confidence intervals.

Myoelectrical activity is responsible for propulsive activity in the fallopian tube (16). This activity facilitates movement of the sperm and ova toward each other and propels the zygote toward the uterine cavity. Estrogen increases smooth muscle activity, and progesterone decreases muscle tone. Aging results in progressive loss of myoelectrical activity along the fallopian tube, which may explain the increased incidence of tubal pregnancy in perimenopausal women (16). Hormonal control of the muscular activity in the fallopian tube may explain the increased incidence of tubal pregnancy associated with failures of the morning-after pill, minipill, progesterone-containing intrauterine devices (IUDs), and ovulation induction. Blighted ova occur more commonly in tubal conceptions than in intrauterine conceptions, although there is no increase in the incidence of chromosomal abnormalities in ectopic pregnancies (18).

Independent factors consistently shown to increase the risk for tubal pregnancy include the following:

- Previous laparoscopically proven PID
- Previous tubal pregnancy

- Current IUD use
- Previous tubal surgery for infertility

Many other risk factors, including contraceptive choice, prior surgery, previous pregnancies, and fertility status, also have been identified.

Pelvic Infection

The relationship of PID, tubal obstruction, and ectopic pregnancy is well documented (13,19). In a study of 415 women with laparoscopically proven PID, the incidence of tubal obstruction increased with successive episodes of PID: 13% after one episode, 35% after two, and 75% after three (19). Furthermore, **after one episode of PID, the ratio of ectopic pregnancy to intrauterine pregnancy was 1 in 24, a sixfold increase over the incidence for women with laparoscopically negative results (1 in 147)**. In a prospective study of 1,204 patients followed until first pregnancy after infection, 47 of 746 (6%) women with laparoscopically documented PID had a tubal gestation, which is significantly higher than the 0.9% incidence that occurred in the control group (20).

Chlamydia is an important pathogen causing tubal damage and subsequent tubal pregnancy. Because many cases of chlamydia salpingitis are indolent, cases may not be recognized or, if recognized, may be treated on an outpatient basis. Chlamydia has been cultured from 7% to 30% of patients with tubal pregnancy (7,21). A strong association between chlamydia infection and tubal pregnancy has been shown with serologic tests for chlamydia (22,23,24,25). Conception is three times as likely to be tubal in women with anti-*Chlamydia trachomatis* titers higher than 1:64 than in those women whose titers were negative (7,26).

Contraceptive Use

Inert and copper-containing IUDs prevent both intrauterine and extrauterine pregnancies (27,28). **Women who conceive with an IUD in place, however, are 0.4 to 0.8 times more likely to have a tubal pregnancy than those not using contraceptives. Because IUDs prevent implantation more effectively in the uterus than in the tube, a woman conceiving with an IUD is 6 to 10 times more likely to have a tubal pregnancy than if she conceives without using contraception (27,28)**.

With copper IUDs, 4% of contraceptive failures are tubal pregnancies. Progesterone IUDs are less effective than copper IUDs in preventing tubal pregnancy; 17% of failures result in tubal pregnancy. Furthermore, the rate of ectopic pregnancy in women using progesterone IUDs is higher than in women not using contraceptives: 1.9 per 100 woman-years (versus 0.5 for copper IUDs) (29). This finding suggests that failures occur for different reasons. Although all IUDs prevent intrauterine implantation, copper IUDs prevent fertilization by cytotoxic and phagocytic effects on the sperm and oocytes. Progesterone-containing IUDs are probably less effective in preventing conception.

Duration of IUD use does not increase the absolute risk for tubal pregnancy (1.2 per 1,000 years of exposure), but with increasing use, there is an increase in the percentage of pregnancies that are tubal (30). With the exception of the Dalkon shield,

for which past use of an IUD is associated with a twofold increased risk (31), the link between past use of IUDs and the risk of tubal pregnancy is unclear. One study showed that previous use of an IUD for longer than 2 years was associated with a fourfold risk, but this risk was present for only the first year after discontinuation of IUD use (27). However, subsequent studies have found no increased risk for tubal pregnancy following IUD use (30,32).

The risk of the pregnancy being ectopic with combination oral contraceptive use has been calculated to be 0.5 to 4% (27,28,33). **Past use of oral contraceptives does not increase the subsequent risk for ectopic pregnancy** (8). Progesterone-only contraceptives, including oral contraceptives (minipill) and subdermal implants (*Norplant*), protect against both intrauterine and ectopic pregnancy when compared with no contraceptive use. If a pregnancy does occur, however, the chance of the pregnancy being ectopic is 4% to 10% for the minipill (34,35) and up to 30% if pregnancy occurs while implants are in place (36,37).

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Condom and diaphragm use protects against both intrauterine and ectopic pregnancy, and there is no increased incidence of ectopic pregnancy (30,33,38).

Sterilization

The greatest risk of pregnancy, including ectopic pregnancy, occurs in the first 2 years after sterilization (39). Despite a greater proportion of poststerilization failures resulting in ectopic pregnancy, the absolute rate of ectopic pregnancy is decreased after sterilization. Calculating cumulative lifetime risk for ectopic pregnancy according to method of contraception, sterilized women have a lower cumulative risk for ectopic pregnancy than IUD users or nonusers of contraception, and women using barrier methods or oral contraceptives have the lowest risk (40).

The risk of tubal pregnancy after any sterilization procedure is 5% to 16% (10,39,40).

The risk depends on the sterilization technique: about one half of postelectrocautery failures are ectopic, compared with 12% after nonlaparoscopic, nonelectrocautery procedures (41). Laparoscopic coagulation has a reduced risk of pregnancy compared with mechanical devices, but the risk of ectopic pregnancy is increased ninefold when a failure does occur (10,42,43).

Tubal repair or reconstruction may be performed to correct an obstruction, lyse adhesions, or evacuate an unruptured ectopic pregnancy. **Although it is clear that tubal surgery is associated with an increased risk for ectopic pregnancy, it is unclear whether the increased risk results from the surgical procedure or from the underlying problem.**

A four- to fivefold increased risk is associated with salpingostomy, neosalpingostomy, fimbrioplasty, anastomosis, and lysis of complex peritubal and periovarian adhesions (7,11,43).

After tubal surgery, the overall rate of ectopic pregnancy is 2% to 7%, and the viable intrauterine pregnancy rate is 50%.

There has been a concern that conservation of the tube at the time of removal of an ectopic pregnancy would increase the risk for recurrent ectopic pregnancy. However, **after either tubal removal or conservation, the rates for intrauterine pregnancy (40%) and ectopic pregnancy (12%) have been found to be identical** (44). In another study, the incidence of ectopic pregnancy could be predicted by the status of the contralateral tube: normal (7%), abnormal (18%), or absent (25%) (42). In a study of pregnancy outcomes of 1,152 patients treated for ectopic pregnancy, preservation of the tube did not increase the incidence of repeat ectopic pregnancy, but it did improve overall fertility rates (45).

Sterilization reversal also increases risk for ectopic pregnancy. The exact risk depends on the method of sterilization, site of tubal occlusion, residual tube length, coexisting disease, and surgical technique. In general, the risk for reanastomosis of a cauterized tube is about 15%,

and it is less than 3% for reversal of Pomeroy or Falope ring procedures (46,47).

Prior Abdominal Surgery

Many patients with ectopic pregnancies have a history of previous abdominal surgery (7,8,48). The role of abdominal surgery in ectopic pregnancy is unclear. In one study, there appeared to be no increased risk for cesarean delivery, ovarian surgery, or removal of an unruptured appendix (49). Other studies have shown that **ovarian cystectomy or wedge resection increases the risk for ectopic pregnancy, presumably because of peritubal scarring** (50,51). Although there is general agreement that an increased risk for ectopic pregnancy is associated with a ruptured appendix (7,43), one study did not confirm this finding (49).

Other Causes

Abortion

There is no established association between ectopic pregnancy and spontaneous abortion (7,9,52). With recurrent abortion (fewer than two consecutive abortions), the risk is increased 2 to 4 times. This may reflect a shared risk factor, such as with luteal

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phase defect. Uncomplicated elective abortion, regardless of the number of procedures or gestational age at which they were performed, is not associated with increased risk (7,8,53,54). In areas with a high incidence of illegal abortion, the risk is increased 10-fold. Presumably, this increased incidence is secondary to postoperative infection and improperly performed procedures (54).

Infertility

Although the incidence of ectopic pregnancy increases with age and parity, there also is a significant increase in nulliparous women undergoing infertility treatment (7,8,44).

For nulliparous women, conceptions after at least 1 year of unprotected intercourse are 2.6 times more likely to be tubal (55). Additional risks for infertile women are associated with specific treatments, including reversal of sterilization, tuboplasty, ovulation induction, and *in vitro* fertilization (IVF).

Hormonal alterations characteristic of *clomiphene citrate* and gonadotropin ovulation-induction cycles may predispose tubal implantation. About 1.1% to 4.6% of conceptions associated with ovulation induction are ectopic pregnancies (8,55). In many of these patients, the results of hysterosalpingography are normal, and there is no evidence of intraoperative tubal pathology. Hyperstimulation, with high estrogen levels, may play a role in tubal pregnancy (56,57); however, not all studies have shown this relationship (58).

The first pregnancy obtained with IVF was a tubal pregnancy (59). About 2% to 8% of IVF conceptions are tubal. Tubal factor infertility is associated with a further increased risk of 17% (60,61,62). Predisposing factors are unclear but may include placement of the embryo high in the uterine cavity, fluid reflux into the tube, and a predisposing tubal factor that prevents the refluxed embryo from returning to the uterine cavity.

Salpingitis Isthmica Nodosa

Salpingitis isthmica nodosa (SIN) is a noninflammatory pathologic condition of the tube in which tubal epithelium extends into the myosalpinx and forms a true diverticulum.

The reported prevalence ranges from 1 in 146 to 11 in 100. **This condition is found more often in the tubes of women with an ectopic pregnancy than in nonpregnant women** (17,63,64). Myometrial electrical activity over the diverticula has been found to be abnormal (16). Whether tubal pregnancy is caused by SIN or whether the association is coincidental is unknown.

Endometriosis or Leiomyomas

Endometriosis or leiomyomas can cause tubal obstruction. However, neither is commonly associated with ectopic pregnancy.

Diethylstilbestrol

Women exposed to *diethylstilbestrol (DES) in utero* who subsequently conceive are at increased risk for ectopic pregnancy. In several case-control studies, these women were more than twice as likely to have a tubal pregnancy (65,66). The Collaborative Diethylstilbestrol-Adenosis Project, which monitored 327 DES-exposed women, found that about 50% had uterine cavity abnormalities (65). In DES-exposed women, the risk for ectopic pregnancy was 13% in those who had uterine abnormalities compared with 4% in those who had a normal uterus. No specific type of defect was related to the risk for ectopic pregnancy.

Smoking

Current cigarette smoking is associated with a more than twofold increased risk for tubal pregnancy (28,51,67,68,69). A case-control study showed a dose relationship: current smokers of more than 20 cigarettes a day had a relative risk of 2.5 compared with nonsmokers, whereas smokers of 1 to 10 cigarettes had a risk of 1.3 (68). Alterations of tubal motility, ciliary activity, and blastocyst implantation are associated with nicotine intake.

Histologic Characteristics

Chorionic villi, usually found in the lumen, are pathognomic findings of tubal pregnancy. Gross or microscopic evidence of an embryo is seen in two thirds of cases

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(70). An unruptured tubal pregnancy is characterized by irregular dilation of the tube, with a blue discoloration caused by hematosalpinx. The ectopic pregnancy may not be readily apparent. Bleeding associated with tubal pregnancies is mainly extraluminal but may be luminal (hematosalpinx) and may extrude from the fimbriated end. A hematoma is frequently seen surrounding the distal segment of the tube. Patients who have tubal pregnancies that spontaneously resolved and those treated with *methotrexate* frequently have an enlargement of the ectopic mass associated with blood clots and extrusion of tissue from the fimbriated end. **Hemoperitoneum is nearly always present but is confined to the cul-de-sac unless tubal rupture has occurred. The natural progression of tubal pregnancy is either expulsion from the fimbriated end (tubal abortion), involution of the conceptus, or rupture, usually around the eighth gestational week.** Some tubal pregnancies form a chronic inflammatory mass that is associated with involution and reestablishment of menses and thus is difficult to diagnose. Extensive histologic sampling may be required to disclose a few ghost villi.

Histologic findings associated with tubal gestation include evidence of chronic salpingitis and SIN. Inflammation associated with salpingitis causes adhesions as a result of fibrin deposition. Healing and cellular organization lead to permanent scarring between folds of tissue.

This scarring may allow transport of sperm but not the passage of the larger blastocyst. About 45% of patients with tubal pregnancies have pathologic evidence of prior salpingitis (71).

The cause of SIN is unknown but is speculated to be an adenomyosis-like process or, less likely, inflammation (72,73). This condition is rare before puberty, indicating a noncongenital origin. Tubal diverticula are identified in about one half of patients who have ectopic pregnancies, as opposed to 5% of women who do not have ectopic pregnancies (17).

Histologic findings include the Arias-Sella reaction, which is characterized by localized hyperplasia of endometrial glands that are hypersecretory (74). The cells have enlarged nuclei that are hyperchromatic and irregular. **The Arias-Sella reaction is a nonspecific finding that can be seen in patients with intrauterine pregnancies** (Fig. 18.2).

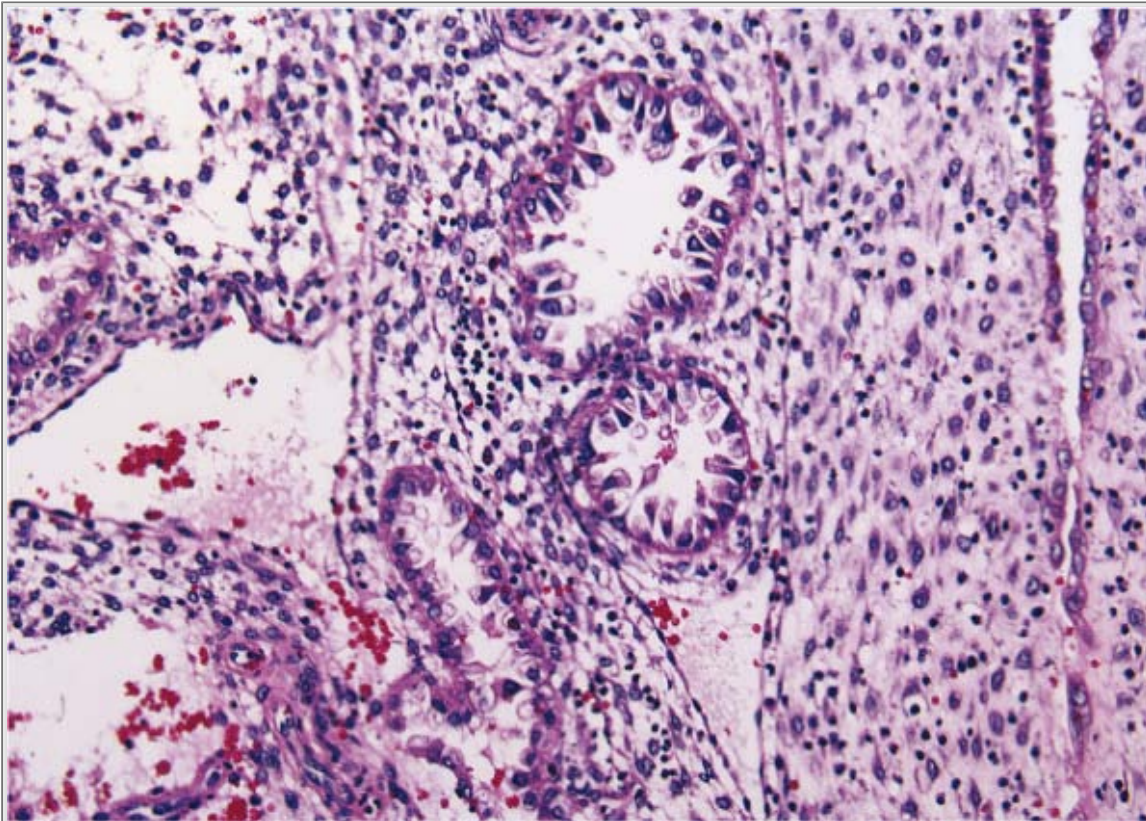


Figure 18.2 The Arias-Stella reaction of the endometrium. The glands are closely packed and hypersecretory with large, hyperchromatic nuclei suggesting malignancy.

Diagnosis

The diagnosis of ectopic pregnancy is complicated by the wide spectrum of clinical presentations, from asymptomatic cases to acute abdomen and hemodynamic shock. The diagnosis and management of a ruptured ectopic pregnancy is straightforward; the primary goal is achieving hemostasis. **If an ectopic pregnancy can be identified before rupture or irreparable tubal damage occurs, consideration may be given to optimizing future fertility.** With patients presenting earlier in the disease process, the number of those without symptoms or with minimal symptoms has increased. Therefore, there must be a high degree of suspicion of ectopic pregnancy, especially in areas of high prevalence. History and physical examination identify patients at risk, improving the probability of detection of ectopic pregnancy before rupture occurs.

HISTORY

Patients who have an ectopic pregnancy generally have an abnormal menstrual pattern or the perception of a spontaneous pregnancy loss. Pertinent points in the history include the menstrual history, previous pregnancy, history of infertility, current contraceptive status, risk factor assessment, and current symptoms.

The classic symptom triad of ectopic pregnancy is pain, amenorrhea, and vaginal bleeding. This symptom group is present in only about 50% of patients, however, and is most typical in patients in whom an ectopic pregnancy has ruptured. Abdominal

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pain is the most common presenting symptom, but the severity and nature of the pain vary widely. There is no pathognomonic pain that is diagnostic of ectopic pregnancy. Pain may be unilateral or bilateral and may occur in the upper or lower abdomen. The pain may be dull, sharp, or crampy and either continuous or intermittent. With rupture, the patient may experience transient relief of the pain, as stretching of the tubal serosa ceases. Shoulder and back pain, thought to result from hemoperitoneal irritation of the diaphragm, may indicate intraabdominal hemorrhage.

Physical Examination

The physical examination should include measurements of vital signs and examination of the abdomen and pelvis. Frequently, the findings before rupture and hemorrhage are nonspecific, and vital signs are normal. The abdomen may be nontender or mildly tender, with or without rebound. The uterus may be slightly enlarged, with findings similar to a normal pregnancy (75). Cervical motion tenderness may or may not be present. **An adnexal mass may be palpable in up to 50% of cases, but the mass varies markedly in size, consistency, and tenderness. A palpable mass may be the corpus luteum and not the ectopic pregnancy.** With rupture and intraabdominal hemorrhage, the patient develops tachycardia followed by hypotension. Bowel sounds are decreased or absent. The abdomen is distended, with marked tenderness and rebound tenderness. Cervical motion tenderness is present. Frequently, the findings of the pelvic examination are inadequate because of pain and guarding.

History and physical examination may or may not provide useful diagnostic information. The accuracy of the initial clinical evaluation is less than 50% (76). Additional tests are frequently required to differentiate early viable intrauterine pregnancy or suspected ectopic or abnormal intrauterine pregnancy.

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Laboratory Assessment

Quantitative β -hCG measurements are the diagnostic cornerstone for ectopic pregnancy. The hCG enzyme immunoassay, with a sensitivity of 25 mIU/mL, is an accurate screening test for detection of ectopic pregnancy. The assay is positive in virtually all documented ectopic pregnancies.

Reference Standards

There are three reference standards for β -hCG measurement. The World Health Organization introduced the First International Standard (1st IS) in the 1930s. Testing for hCG and its subunits have improved over the years. The Second International Standard (2nd IS), introduced in 1964, has varying amounts of β -hCG and β subunits. A purified preparation of

β -hCG is now available. Originally referred to as the First International Reference Preparation (1st IRP), the test standard is now referred to as the Third International Standard (3rd IS). Although each standard has its own scale, as a general rule, the 2nd IS is about one half of the 3rd IS. For example, if a level is reported as 500 mIU/mL (2nd IS), it is equivalent to a level of 1,000 mIU/mL (3rd IS). The assay standard used must be known to interpret hCG results correctly (77). In several recent articles, attention has been drawn to a problem known **as phantom hCG, in which the presence of heterophile antibodies or proteolytic enzymes causes a false-positive hCG result**. Because the antibodies are large glycoproteins, significant quantities of the antibody are not excreted in the urine. Thus, **in the patient with hCG levels less than 1,000 mIU/mL, a urine pregnancy test should be performed and confirmatory positive results obtained before instituting treatment** (78,79).

Doubling Time

The hCG level correlates somewhat with the gestational age (80). During the first 6 weeks of amenorrhea, serum hCG levels increase exponentially. Thus, during this period, the doubling time of hCG is relatively constant, regardless of the initial level. After the sixth week of gestation, when hCG levels are higher than 6,000 to 10,000 mIU/mL, the hCG rise is slower and not constant (81).

The hCG doubling time can help to differentiate an ectopic pregnancy from an intrauterine pregnancy—a 66% rise in the hCG level over 48 hours (85% confidence level) represents the lower limit of normal values for viable intrauterine pregnancies (82). About 15% of patients with viable intrauterine pregnancies have less than a 66% rise in hCG level over 48 hours, and a similar percentage with an ectopic pregnancy have more than a 66% rise. If the sampling interval is reduced to 24 hours, the overlap between normal and abnormal pregnancies is even greater. Patients with normal intrauterine pregnancies usually have more than a 50% rise in their hCG levels over 48 hours when the starting level is less than 2,000 mIU/mL. **The hCG pattern that is most predictive of an ectopic pregnancy is one that has reached a plateau (a doubling time of more than 7 days). For falling levels, a half-life of less than 1.4 days is rarely associated with an ectopic pregnancy, whereas a half-life of more than 7 days is most predictive of ectopic pregnancy.**

Serial hCG levels are usually required when the results of the initial ultrasonography examination are indeterminate (i.e., when there is no evidence of an intrauterine gestation or extrauterine cardiac activity consistent with an ectopic pregnancy). When the hCG level is less than 2,000, doubling time helps to predict viable intrauterine gestation (normal rise) versus nonviability (subnormal rise). With normally rising levels, a second ultrasonography examination is performed when the level is expected (by extrapolation) to reach 2,000 mIU/mL. Abnormally rising levels (less than 2,000 mIU/mL and less than 50% rise over 48 hours) indicate a nonviable pregnancy. The location (i.e., intrauterine versus extrauterine) must be determined surgically, either by laparoscopy or dilation and curettage. Indeterminate ultrasonography results, and an hCG

level of less than 2,000 mIU/mL is diagnostic of nonviable gestation, either ectopic pregnancy or a complete abortion. In general, rapidly falling hCG levels (50% over 48 hours) occur with a completed abortion, whereas with an ectopic pregnancy levels rise or plateau.

Single hCG Level

A single hCG measurement has limited usefulness because there is considerable overlap of values between normal and abnormal pregnancies at a given gestational age.

The ectopic pregnancy site and hCG level do not correlate (83). Also, many patients in whom the diagnosis of ectopic pregnancy is being considered are uncertain about their menstrual dates. A single hCG level may be useful when measured by sensitive enzyme immunoassays that, if negative, exclude a diagnosis of ectopic pregnancy. Measurement of a single level may also be helpful in predicting pregnancy outcome after timed conceptions using advanced reproductive technology. If the hCG level is more than 300 mIU/mL on day 16 to 18 after artificial insemination, there is an 88% chance of a live birth (84). If the hCG level is less than 300 mIU/mL, the chance of a live birth is only 22%. Also, a single hCG level may facilitate the interpretation of ultrasonography when an intrauterine gestation is not visualized.

An hCG level greater than the ultrasound discriminatory zone indicates a possible extrauterine pregnancy. However, determination of serial hCG levels may be needed to differentiate an ectopic pregnancy from a completed abortion. Further tests are required for patients in whom ultrasonography examination results are inconclusive and hCG levels are below the discriminatory zone.

Serum Progesterone

In general, the mean serum progesterone level in patients with ectopic pregnancies is lower than that in patients with normal intrauterine pregnancies (85,86). However, in studies of more than 5,000 patients with first-trimester pregnancies, a spectrum of progesterone levels has been found in patients with both normal and abnormal pregnancies (87,88,89). About 70% of patients with a viable intrauterine pregnancy have serum progesterone levels higher than 25 ng/mL, whereas only 1.5% of patients with ectopic pregnancies have serum progesterone levels higher than 25 ng/mL, and most of these pregnancies exhibit cardiac activity (87,88,89).

A serum progesterone level can be used as an ectopic pregnancy screening test for both normal and abnormal pregnancy, particularly in settings in which hCG levels and ultrasonography are not readily available. A serum progesterone level of less than 5 ng/mL is highly suggestive of an abnormal pregnancy, but it is not 100% predictive. The risk of a normal pregnancy with a serum progesterone level of less than 5 ng/mL is about 1 in 1,500 (90). Thus, serum progesterone measurements alone cannot be used to predict pregnancy nonviability.

Other Endocrinologic Markers

In an effort to improve early detection of ectopic pregnancy, various endocrinologic and protein markers have been studied. Estradiol levels increase slowly from conception until 6 weeks of gestation and then rise rapidly as placental production of estradiol increases (91). Estradiol levels are significantly lower in ectopic pregnancies when compared with viable pregnancies. However, there is considerable overlap between normal and abnormal pregnancies as well as between intrauterine and extrauterine pregnancies (92,93).

Maternal serum creatine kinase has been studied as a marker for ectopic pregnancy diagnosis (94). Maternal serum creatine kinase levels were significantly higher in all patients with tubal pregnancy when compared with those in patients who had missed abortions or normal intrauterine pregnancies. No correlation was found between the creatine kinase level and the clinical presentation of the patient, however, and there was no correlation with the hCG levels. *Schwangerschafts protein 1* (SP₁), also known as pregnancy-associated plasma protein C (PAPP-C) or pregnancy-specific β glycoprotein (PSBS), is produced by the syncytiotrophoblast (92). The main advantage of SP₁ level assessment may be in the diagnosis of conception after recent hCG administration. A level of 2 ng/L might be used

for the diagnosis of pregnancy; however, it is doubtful that a diagnosis can be established before delay of menses. Although the level of SP₁ increases late in all patients with a nonviable pregnancy, a single SP₁ level assessment does not have prognostic value (95).

Relaxin is a protein hormone produced solely by the corpus luteum of pregnancy. It appears in the maternal serum at 4 to 5 weeks of gestation, peaks at about 10 weeks of gestation, and decreases until term (96). Relaxin levels are significantly lower in ectopic pregnancies and spontaneous abortions than in normal intrauterine pregnancies. Prorenin and active renin levels are significantly higher in viable intrauterine pregnancies than in either ectopic pregnancies or spontaneous abortions, with a single level of more than 33 pg/mL excluding the diagnosis of ectopic pregnancy (97). However, the clinical utility of relaxin, prorenin, and renin levels in diagnosing ectopic pregnancy has not yet been determined.

CA125 is a glycoprotein, the origin of which is uncertain during pregnancy. Levels of CA125 rise during the first trimester and return to a nonpregnancy range during the second and third trimesters. After delivery, maternal serum concentrations increase (98,99). Levels of CA125 have been studied in an effort to predict spontaneous abortion. Although a positive correlation has been found between elevated CA125 levels 18 to 22 days after conception and spontaneous abortion, repeat measurements at 6 weeks of gestation did not correlate with outcome (100). Conflicting results have been reported—one study showed a higher serum CA125 level in normal than in ectopic pregnancies 2 to 4 weeks after a missed menses, whereas another study found higher CA125 levels for ectopic pregnancies compared with normal pregnancies (101,102).

Maternal serum a-fetoprotein (AFP) levels are elevated in ectopic pregnancies (103,104); however, the use of AFP measurements as a screening technique for ectopic pregnancy has not been studied. A combination of AFP with three other markers— β -hCG, progesterone, and estradiol—has 98.5% specificity and 94.5% accuracy for the prediction of ectopic pregnancy.

C-reactive protein is an acute-phase reactant that increases with trauma or infection. Levels of this protein are lower in patients with ectopic pregnancy than in patients with an acute infectious process. Thus, when an infectious process is part of the differential diagnosis, measurement of C-reactive protein may be beneficial (105).

Ultrasonography

Improvements in ultrasonography have resulted in the earlier diagnosis of intrauterine and ectopic gestations (106). However, **the sensitivity of the β assay usually allows the diagnosis of pregnancy before direct visualization by ultrasonography.**

The complete examination should include both transvaginal and transabdominal ultrasonography. **Transvaginal ultrasonography is superior to transabdominal ultrasonography in evaluating intrapelvic structures.** The closeness of the vaginal probe to the pelvic organs allows use of higher frequencies (5–7 mHz), which improves resolution. **Intrauterine pregnancy can be diagnosed 1 week earlier with transvaginal than with transabdominal ultrasonography.** Evidence of an empty uterus, detection of adnexal masses and free peritoneal fluid, and direct signs of ectopic pregnancy are more reliably established with a transvaginal procedure (107,108,109,110,111). Transabdominal ultrasonography permits visualization of both the pelvis and abdominal cavity and should be included as part of the complete ectopic pregnancy evaluation to detect adnexal masses and hemoperitoneum.

The earliest ultrasonographic finding of an intrauterine pregnancy is a small fluid space and the gestational sac, surrounded by a thick echogenic ring, located

eccentrically within the endometrial cavity. The earliest normal gestational sac is seen at 5 weeks of gestation with transabdominal ultrasonography and at 4 weeks of gestation with transvaginal ultrasonography (112). As the gestational sac grows, a yolk sac is seen within it, followed by an embryo with cardiac activity.

The appearance of a normal gestational sac may be simulated by intrauterine fluid collection, the pseudogestational sac, which occurs in 8% to 29% of patients with ectopic pregnancy (113,114,115). This ultrasonographic lucency, centrally located, probably represents bleeding into the endometrial cavity by the decidual cast. Clots within this lucency may mimic a fetal pole.

Morphologically, identification of the double decidual sac sign (DDSS) is the best method of ultrasonographically differentiating true sacs from pseudosacs (116). The double sac, believed to be the decidua capsularis and parietalis, is seen as two concentric echogenic rings separated by a hypoechogenic space. Although useful, this approach has some limitations in sensitivity and specificity—the DDSS sensitivity ranges from 64% to 95% (115). Pseudosacs may occasionally appear as the DDSS; intrauterine sacs of failed pregnancies may appear as pseudosacs.

The appearance of a yolk sac within the gestational sac is superior to the DDSS in confirming intrauterine pregnancy (117). The yolk sac is consistently visible on transabdominal ultrasonography with a gestational sac size of 2 cm and on transvaginal ultrasonography with a gestational sac size of 0.6 to 0.8 cm (118,119). Intrauterine sacs smaller than 1 cm on transabdominal ultrasonography and smaller than 0.6 cm on transvaginal ultrasonography are considered indeterminate. Larger sacs without DDSS or yolk sac represent either a failed intrauterine or ectopic pregnancy.

The presence of cardiac activity within the uterine cavity is definitive evidence of an intrauterine pregnancy. This finding essentially eliminates the diagnosis of ectopic pregnancy because the incidence of combined intrauterine and extrauterine pregnancy is 1 in 30,000.

The presence of an adnexal gestational sac with a fetal pole and cardiac activity is the most specific but least sensitive sign of ectopic pregnancy, occurring in only 10% to 17% of cases (105,120,121). The recognition of other characteristics of ectopic pregnancy has improved ultrasonographic sensitivity. Adnexal rings (fluid sacs with thick echogenic rings) that have a yolk sac or nonliving embryo are accepted as specific ultrasonographic signs of ectopic pregnancy (122). Adnexal rings are visualized in 22% of ectopic pregnancies using transabdominal ultrasonography and in 38% using transvaginal ultrasonography (107). Other studies have identified adnexal rings in 33% to 50% of ectopic pregnancies (105,121). The adnexal ring may not always be apparent because bleeding around the sac results in the appearance of a nonspecific adnexal mass.

Complex or solid adnexal masses are frequently associated with ectopic pregnancy (1,3,19); however, the mass may represent a corpus luteum, endometrioma, hydrosalpinx, ovarian neoplasm (e.g., dermoid cyst), or pedunculated fibroid. The presence of free cul-de-sac fluid is frequently associated with ectopic pregnancy and is no longer considered evidence of rupture. The presence of intraabdominal free fluid should raise concern about tubal rupture (123).

Accurate interpretation of ultrasonography findings requires correlation with the hCG level (discriminatory zone) (114,119,122,124). All viable intrauterine pregnancies can be visualized by transabdominal ultrasonography for serum hCG levels higher than 6,500 mIU/mL; none can be seen at 6,000 mIU/mL. The inability to detect an intrauterine gestation with serum hCG levels higher than 6,500 mIU/mL indicates

the presence of an abnormal (failed intrauterine or ectopic) pregnancy. Intrauterine sacs seen at hCG levels below the discriminatory zone are abnormal and represent either failed intrauterine pregnancies or the pseudogestational sacs of ectopic pregnancy. If there is no definite sign of an intrauterine gestation (the empty uterus sign) and the hCG level is below the discriminatory zone, the differential diagnosis includes the following considerations:

- Normal intrauterine pregnancy too early for visualization
- Abnormal intrauterine gestation
- Recent abortion
- Ectopic pregnancy
- Nonpregnant patient

The discriminatory zone has been lowered progressively with improvements in ultrasonography resolution. **Discriminatory zones for transvaginal ultrasonography have been reported at levels from 1,000 to 2,000 mIU/mL** (114,119,122,124). Discriminatory zones vary according to the expertise of the examiner and capability of the equipment.

Although the discriminatory zone for intrauterine pregnancy is well established, there is no such zone for ectopic pregnancy. Levels of hCG have not been shown to correlate with the size of ectopic pregnancy. Regardless of how high the hCG level may be, nonvisualization does not exclude ectopic pregnancy. An ectopic pregnancy may be present anywhere in the abdominal cavity, making ultrasonographic visualization difficult.

Doppler Ultrasonography

A Doppler shift occurs whenever the source of an ultrasound beam is moving. The usual sources of Doppler-shifted frequencies are red blood cells. The presence of intravascular blood flow, flow direction, and flow velocity can be determined (125). Pulsed Doppler provides ultrasonographic control over which vessels are sampled. The vascular information is provided both by the shape of the time-velocity waveform (high- or low-resistance flow) and by its systolic, diastolic, and mean velocities (or Doppler frequency shifts) (126). Color-flow Doppler ultrasonography analyzes very-low-amplitude signals from an entire ultrasound tomogram; the Doppler shift is then modulated into color. This information is used to gauge generalized tissue vascularity and to guide pulsed Doppler vascular sampling of specific vessels.

The waveform in the uterine arteries in the nongravid state and in the first trimester of pregnancy shows a high-resistance (little or no diastolic flow), low-velocity pattern. Conversely, a high-velocity, low-resistance signal is localized to the area of developing placentation (127,128,129). This pattern, seen near the endometrium, is associated with normal and abnormal intrauterine pregnancies and is termed *peritrophoblastic flow*. Whereas transvaginal ultrasonography requires a well-developed double decidual sac (or possibly cardiac activity) to localize an intrauterine gestation, the use of Doppler techniques allows

detection of an intrauterine pregnancy at an earlier date. The combined use of Doppler and two-dimensional imaging allows the differentiation of pseudogestational sacs and true intrauterine gestational sacs (130) and the differentiation of the empty uterus sign as either the presence of an intrauterine pregnancy (normal and abnormal) or absence of an intrauterine pregnancy (with an increased risk for ectopic pregnancy) (123).

A similar high-velocity, low-impedance flow characterizes ectopic pregnancies. The addition of Doppler to the ultrasonographic evaluation of suspected ectopic pregnancy improves diagnostic sensitivity for individual diagnoses: from 71% to 87% for ectopic pregnancy, from 24% to 59% for failed intrauterine pregnancy, and from 90% to 99% for normal intrauterine pregnancy (122,123,130).

Dilation and Curettage

Uterine curettage is performed when the pregnancy has been confirmed to be nonviable and the location of the pregnancy cannot be determined by ultrasonography. The decision to evacuate the uterus in the presence of a positive pregnancy test must be made with caution to avoid the unintentional disruption of a viable intrauterine pregnancy.

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Although suction curettage traditionally has been performed in the operating room, it can now be accomplished under local anesthesia on an outpatient basis. Endometrial sampling methods (e.g., a Novak curettage or Pipelle endometrial sampling device) are accurate in diagnosing abnormal uterine bleeding, but their reliability for intrauterine pregnancy evacuation has not been studied. These devices might miss intrauterine villi and falsely suggest the diagnosis of ectopic pregnancy.

It is essential to confirm the presence of trophoblastic tissue as rapidly as possible so that therapy may be instituted. Once tissue is obtained by curettage, it can be added to saline, in which it will float (Fig. 18.3). Decidual tissue does not float. Chorionic villi are usually identified by their characteristic lacy frond appearance. The sensitivity and specificity of this technique are 95% when the tissue is examined with the aid of a dissecting microscope. Because flotation of curettage sample tissue is not 100% accurate in differentiating an intrauterine from extrauterine gestation, histologic confirmation or serial β -hCG level measurement is required. The presence of chorionic villi may be assessed rapidly with frozen section analysis, which avoids the waiting period of at least 48 hours for permanent histologic evaluation. Immunocytochemical staining techniques have been used to identify intermediate trophoblasts that are not normally identified by light microscopy (74).

When frozen section analysis is not available, serial assessment of hCG levels permits rapid diagnosis. After evacuation of an abnormal intrauterine pregnancy, the hCG level decreases by greater than 15% within 12 to 24 hours. A borderline fall may represent

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interassay variability. A repeat level should be obtained in 24 to 48 hours to confirm the decline. If the uterus is evacuated and the pregnancy is extrauterine, the hCG level plateaus or continues to increase, indicating the presence of extrauterine trophoblastic tissue.

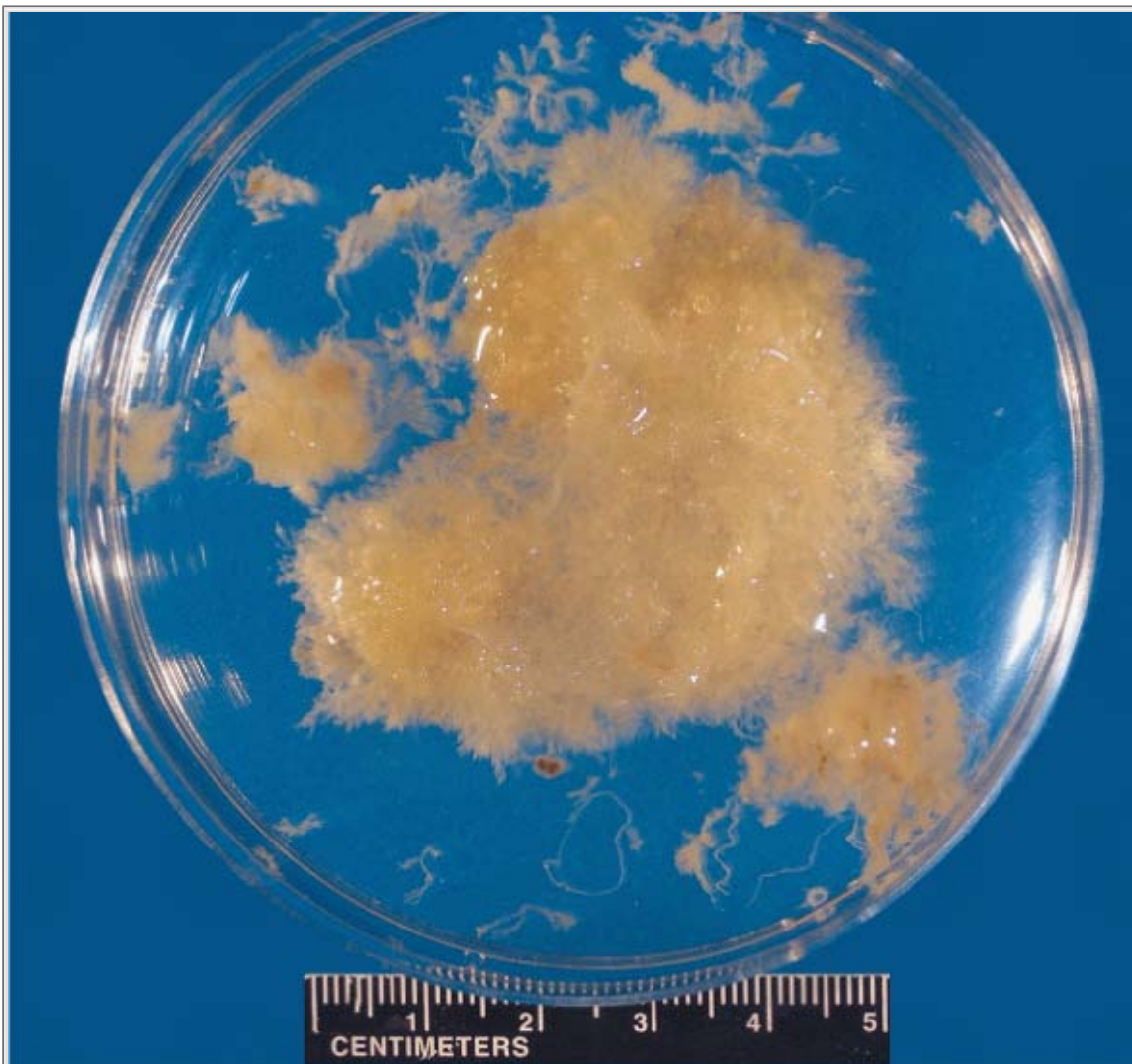


Figure 18.3 When floated in saline, chorionic villi are often readily distinguishable as lacy fronds of tissue. (From **Stovall TG, Ling FW.** *Extrauterine pregnancy: clinical diagnosis and management.* New York, NY: McGraw-Hill, 1993:186, with permission.)

Culdocentesis

Culdocentesis has been used widely as a diagnostic technique for ectopic pregnancy. With the use of hCG testing and transvaginal ultrasonography, however, culdocentesis is rarely indicated. The purpose of the procedure is to determine the presence of nonclotting blood, which increases the likelihood of ruptured ectopic pregnancy. After exposing the posterior vaginal fornix with a bivalve vaginal speculum, the posterior lip of the cervix is grasped with a tenaculum. The cul-de-sac is then entered through the posterior vaginal wall with an 18- to 20-gauge spinal needle with a syringe attached. As the cul-de-sac is entered, suction is applied, and the intraperitoneal contents are aspirated. If nonclotting blood is obtained, the results are positive. If serous fluid is present, results are negative. A lack of fluid return or clotted blood is nondiagnostic.

Historically, if the culdocentesis results were positive, laparotomy was performed for a presumed diagnosis of ruptured tubal pregnancy. However, **the results of culdocentesis do not always correlate with the status of the pregnancy.** Although about 70% to 90% of patients with ectopic pregnancy have a hemoperitoneum demonstrated by culdocentesis, only 50% of patients have a ruptured tube (131). Furthermore, about 6% of women with positive culdocentesis results do not have an ectopic gestation at the time of

laparotomy. Nondiagnostic taps occur in 10% to 20% of patients with ectopic pregnancy and, therefore, are not definitive of the diagnosis.

Laparoscopy

Laparoscopy is the gold standard for the diagnosis of ectopic pregnancy. Generally, the fallopian tubes are easily visualized and evaluated, although the diagnosis of ectopic pregnancy is missed in 3% to 4% of patients who have very small ectopic gestations. The ectopic gestation usually is seen distorting the normal tubal architecture. With earlier diagnosis, the possibility that a small ectopic pregnancy may not be visualized increases. Pelvic adhesions or previous tubal damage may compromise assessment of the tube. False-positive results occur when tubal dilation or discoloration is misinterpreted as an ectopic pregnancy, in which case the tube can be incised unnecessarily and damaged.

Diagnostic Algorithm

The presenting symptoms and physical findings of patients with unruptured ectopic pregnancies are similar to those of patients with normal intrauterine pregnancies (89). History, risk-factor assessment, and physical examination are the initial steps in the management of suspected ectopic pregnancy. Patients in a hemodynamically unstable condition should undergo immediate surgical intervention. Patients with a stable, relatively asymptomatic condition may be assessed as outpatients.

If the diagnosis of ectopic pregnancy can be confirmed without laparoscopy, several potential benefits result. First, both the anesthetic and surgical risks of laparoscopy are avoided; second, medical therapy becomes a treatment option. Because many ectopic pregnancies occur in histologically normal tubes, resolution without surgery may spare the tube from additional trauma and improve subsequent fertility. **An algorithm for the diagnosis of ectopic pregnancy without laparoscopy proved to be 100% accurate in a randomized clinical trial** (132,133) (Fig. 18.4). This screening algorithm shows the combined use of history and physical examination, serial hCG levels, serum progesterone levels, vaginal ultrasonography, and dilation and curettage. When hCG levels and transvaginal ultrasonography are available in a timely fashion, serum progesterone screening is not required. Serial hCG levels are used to assess pregnancy viability, correlated with transvaginal ultrasonography findings, and measured serially after a suction curettage. For patients in a stable condition, a treatment decision is never based on a single hCG level. After the initial evaluation, the patient

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is seen again at 24 to 48 hours for a repeat hCG level. At this time, transvaginal ultrasonography often is repeated so the findings can be correlated with the two hCG levels.

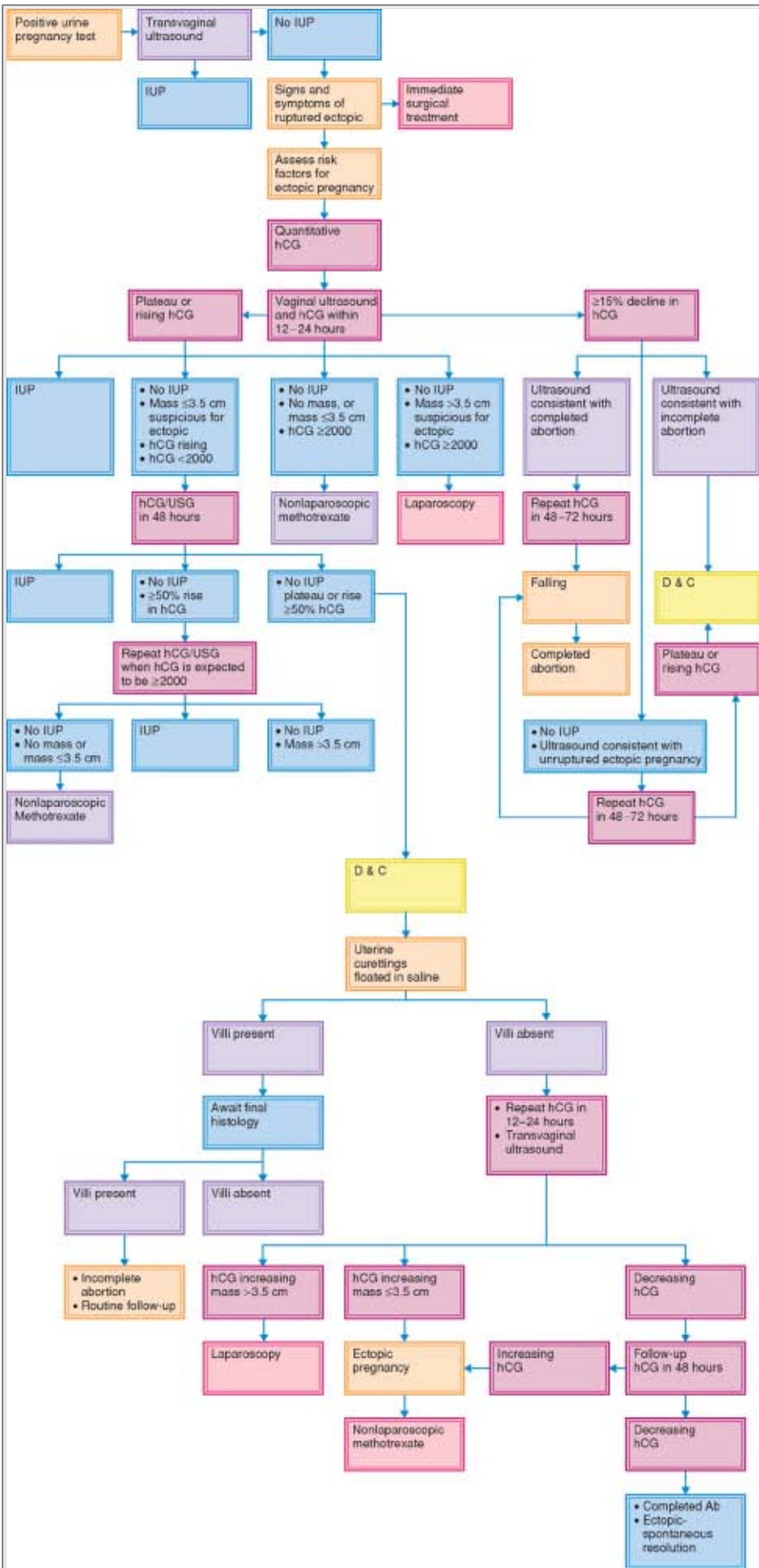


Figure 18.4 Nonlaparoscopic algorithm for diagnosis of ectopic pregnancy. hCG, human chorionic gonadotropin; IUP, Intrauterine pregnancy; USG, Urine specific gravity; D & C, dilation and curettage.

In this algorithm, **transvaginal ultrasonography is used as follows:**

- The identification of an intrauterine gestational sac or pregnancy effectively excludes the presence of an extrauterine pregnancy. If the patient has a rising hCG level of more than 2,000 mIU/mL, and no intrauterine gestational sac is identified, the patient is considered to have an extrauterine pregnancy and can be treated without further testing.
- Adnexal cardiac activity, when seen, definitively confirms the diagnosis of ectopic pregnancy.
- A tubal mass as small as 1 cm can be identified and characterized. Masses greater than 3.5 cm with cardiac activity or larger than 4 cm without cardiac activity should not be treated with medical therapy.

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Suction curettage is used to differentiate nonviable intrauterine pregnancies from ectopic gestations (less than 50% rise in hCG level over 48 hours, an hCG level of less than 2,000 mIU/mL, and indeterminate ultrasonography findings). Performance of this procedure avoids unnecessary use of methotrexate in patients with abnormal intrauterine pregnancy that can be diagnosed only by evacuating the uterus. An unlikely potential problem with suction curettage is missing either an early nonviable intrauterine pregnancy or combined intrauterine and extrauterine pregnancies.

Treatment

Ectopic pregnancy can be treated either medically or surgically. Both methods are effective, and the choice depends on the clinical circumstances, the site of the ectopic pregnancy, and the available resources.

Surgical Treatment

Operative management is the most widely used treatment for ectopic pregnancy. There has been debate about which surgical procedure is best. Salpingo-oophorectomy was once considered appropriate because it was theorized that this technique would eliminate transperitoneal migration of the ovum or zygote, which was thought to predispose to recurrent ectopic pregnancy (134). Ovarian removal results in all ovulations occurring on the side with the remaining normal fallopian tube. Subsequent studies have not confirmed that ipsilateral oophorectomy increases the likelihood of conceiving an intrauterine pregnancy; therefore, this practice is not recommended (135).

Salpingectomy Versus Salpingostomy

Linear salpingostomy is currently the procedure of choice when the patient has an unruptured ectopic pregnancy and wishes to retain her potential for future fertility.

The products of conception are removed through an incision made into the tube on

its antimesenteric border. The procedure can be accomplished with a needle-tip cautery, laser, scalpel, or scissors. It can be done with operative laparoscopic techniques or laparotomy. In a study in which patients treated with either salpingectomy or salpingostomy were followed for a period of 3 years to about 12.5 years, there was no difference in pregnancy rates (136). A history of infertility is the most significant determinant of future fertility, and such patients probably are served better by salpingectomy to decrease their subsequent chance of a recurrent ectopic pregnancy. Linear salpingostomy is as effective as segmental resection with primary reanastomosis, even for ectopic pregnancies occurring in the isthmic tubal segment, and it is technically less difficult and has a shorter operative time (137).

Milking the tube to effect a tubal abortion has been advocated; if the pregnancy is fimbrial, this technique may be effective. However, when milking was compared with linear salpingostomy for ampullary ectopic pregnancies, milking was associated with a twofold increase in the recurrent ectopic pregnancy rate (138).

Laparotomy Versus Laparoscopy

Salpingostomy, salpingectomy, or segmental resection can be accomplished by laparoscopy or laparotomy. The approach used depends on the hemodynamic stability of the patient, the size and location of the ectopic mass, and the surgeon's expertise. **Laparotomy is indicated when the patient becomes hemodynamically unstable, whereas laparoscopy is reserved for patients who are hemodynamically stable. A**

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ruptured ectopic pregnancy does not necessarily require laparotomy. However, if large blood clots are present or the intraabdominal blood cannot be evacuated in a timely manner, laparotomy should be considered. Cornual or interstitial pregnancies often require laparotomy, although laparoscopic management has been described (139). Laparotomy is chosen for the management of most ovarian and abdominal pregnancies. In some cases, the patient may have extensive abdominal or pelvic adhesive disease, making laparoscopy difficult and laparotomy more feasible.

Laparoscopy has advantages over laparotomy for management of ectopic pregnancy. In a case-control study of 50 patients comparing the use of laparoscopy and laparotomy for ectopic pregnancy management, hospital stay was significantly shorter (1.3 ± 0.8 versus 3.0 ± 1.1 days), operative time was shorter (78 ± 26 versus 104 ± 27 minutes), and convalescence was shorter (9 ± 8 versus 26 ± 16 days) in the laparoscopy group (140). In a randomized study in which 30 patients in each group were compared, patients undergoing laparoscopic management had less estimated blood loss, shorter hospital stay, equivalent tubal pregnancy rates, and similar pregnancy and persistent trophoblast rates (141). In another study, patients were assigned during alternate months to undergo laparoscopic management ($N = 26$) or laparotomy ($N = 37$) (142). There were no differences in operative time, although patients undergoing laparoscopy had a significant decrease in blood loss, postoperative hospital stay, narcotic requirement, and time to return to normal activity.

Laparoscopic management was associated with significant cost savings when compared with laparotomy (more than $\$5,528 \pm \$1,586$ versus more than $\$6,793 \pm \155). Using a prospective analysis, 105 patients with tubal pregnancy were stratified with regard to age and risk factors and then randomized to undergo either laparoscopic management or laparotomy (143). Subsequently, 73 patients underwent second-look laparoscopy to assess the degree of adhesion formation. Patients treated by laparotomy had significantly more adhesions at the surgical site than those treated by laparoscopy, but tubal patency rates were similar. Pregnancy rates were not analyzed.

Reproductive Outcome

Reproductive outcome after ectopic pregnancy usually is evaluated by determining tubal patency by hysterosalpingography, the subsequent intrauterine pregnancy rate, and the recurrent ectopic pregnancy rate. **Pregnancy rates are similar in patients treated by either laparoscopy or laparotomy. Tubal patency on the ipsilateral side after conservative laparoscopic management is about 84%.**

In a study of 143 patients followed after undergoing laparoscopic procedures for ectopic pregnancy, the overall intrauterine pregnancy rates for laparoscopic salpingostomy (60%) and laparoscopic salpingectomy (54%) were not significantly different (144). If the patient had evidence of tubal damage, pregnancy rates (42%) were significantly lower than in those women who did not have tubal damage (79%). In another study, the reproductive outcome of 188 patients followed for a mean of 7.2 years (range 3–15 years) was reported after conservation by laparotomy for ectopic pregnancy (145). An intrauterine pregnancy occurred in 83 (70%) patients, with a recurrent ectopic pregnancy rate of 13%, suggesting that reproductive outcome after an ectopic pregnancy treated by laparotomy is similar to that of patients undergoing laparoscopic or medical management. Thus, when compared with medical therapy, surgical management appears to have equal reproductive outcome, although a prospective randomized trial has not been reported.

Medical Treatment

The drug most frequently used for medical management of ectopic pregnancy is methotrexate, although other agents have been studied, including potassium chloride (KCl), hyperosmolar glucose, prostaglandins, and *RU-486*. These agents may be given systemically (intravenously, intramuscularly, or orally) or locally (laparoscopic direct injection, transvaginal ultrasonographically directed injection, or retrograde salpingography).

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Methotrexate

Methotrexate is a folic acid analogue that inhibits dehydrofolate reductase and thereby prevents synthesis of DNA. It has been used extensively in the treatment of gestational trophoblastic disease (see Chapter 37). **Commonly reported side effects include leukopenia, thrombocytopenia, bone marrow aplasia, ulcerative stomatitis, diarrhea, and hemorrhagic enteritis.** Other reported side effects include alopecia, dermatitis, elevated liver enzyme levels, and pneumonitis (146). However, **no significant side effects have been reported at the low doses used for ectopic pregnancy treatment. Minor side effects have been reported with multiple doses;** *citrovorum factor* reduces the incidence of these side effects and is generally used when prolonged treatment is required. Importantly, long-term follow-up of women treated with *methotrexate* for gestational trophoblastic disease shows no increase in congenital malformations, spontaneous abortions, or tumors recurring after chemotherapy (147). Treatment of ectopic pregnancy differs from that of gestational trophoblastic disease in that a smaller total dose of *methotrexate* is required and shorter treatment duration is used.

Initially, *methotrexate* was used for the treatment of trophoblastic tissue left *in situ* after exploration for an abdominal pregnancy (148). In 1982, Tanaka and colleagues treated an unruptured interstitial gestation with a 15-day course of intramuscular *methotrexate* (149). The use of *methotrexate* for primary treatment of ectopic pregnancy has been reported in more than 300 patients (150,151,152,153,154,155,156,157,158,159).

A trial of **intramuscular methotrexate (1 mg/kg/day) followed by citrovorum factor (0.1 mg/kg/day) on alternate days was given to 100 patients with a success rate of 96%** (153,155). This outpatient treatment protocol used *methotrexate* plus *citrovorum factor* given only until the hCG level began to decline. Treatment was given until there was at least a 15% decline between two consecutive daily hCG levels. *Citrovorum factor* is given on the day after the *methotrexate* is administered, even if no further *methotrexate* is indicated. Once *methotrexate* is discontinued, hCG levels are measured weekly until the results are negative. A second course of *methotrexate* plus *citrovorum factor* is given only if there is a plateau or rise in the hCG level. Of the 96 patients successfully treated, 17 required only one *methotrexate* and *citrovorum factor* dose, and 19 required four doses. Four patients treated with *methotrexate* failed therapy and required surgical treatment for tubal rupture, and each of these cases differed with respect to ectopic pregnancy size, hCG level, and time of rupture. Of five ectopic pregnancies with cardiac activity, four were successfully treated. No conclusions can be drawn regarding risk factors or predictors of ectopic pregnancy rupture.

Methotrexate was administered to 31 patients for treatment of ectopic pregnancy in a single-dose intramuscular injection of 50 mg/m² without *citrovorum factor*. Of 30 evaluable patients, 29 (96.7%) were successfully treated, and no patients experienced *methotrexate*-related side effects. Some 500 patients have now been treated using the single-dose protocol outlined in Table 18.3 (160). **Compared with the multidose protocol, single-dose methotrexate is less expensive, patient acceptance is greater because less monitoring is required during treatment, the incidence of side effects is decreased, and the treatment results and prospects for future fertility are comparable.**

Table 18.3 Single-dose Methotrexate Protocol for Ectopic Pregnancy

<i>Day</i>	<i>Therapy^a</i>
0	D & C, hCG
1	CBC, SGOT, BUN, creatinine, blood type and Rh
4	<i>Methotrexate</i> 50 mg/m ² IM
7	hCG

D & C, dilation and curettage; hCG, human chorionic gonadotropin; CBC, complete blood count; SGOT, serum glutamic-oxaloacetic transaminase; BUN, blood urea nitrogen; IM, intramuscularly.

^aIf less than a 15% decline in hCG level between days 4 and 7, give second dose of *methotrexate*, 50 mg/m², on day 7.

If more than a 15% decline in hCG level between days 4 and 7, follow weekly until hCG is below 10 mIU/mL.

In patients not requiring D & C (hCG > 2,000 mIU/mL and no gestational sac on transvaginal ultrasonography), days 0 and 1 are combined.

Initiating Methotrexate

Outlined in Table 18.4 is a checklist that should be followed by the physician before initiating *methotrexate*. It also includes instructions that are helpful to the patient.

Table 18.4 Initiation of Methotrexate: Physician Checklist and Patient Instructions

Physician Checklist

Obtain hCG level.

Perform transvaginal ultrasound within 48 hours.

Perform endometrial curettage if hCG level is less than 2,000 mIU/mL.

Obtain normal liver function (SGOT), normal renal function (BUN, creatinine), and a normal CBC (WBC < 2,000/mL and platelet count > 100,000)

Administer *RhoGAM* if patient is Rh-negative.

Identify unruptured ectopic pregnancy smaller than 3.5 cm.

Obtain informed consent.

Prescribe FeSO₄ 325 mg PO bid if hematocrit is less than 30%.

Schedule follow-up appointment on days 4, 6, and 7.

Patient Instructions

Refrain from alcohol use, multivitamins containing folic acid, and sexual intercourse until hCG level is negative.

Call your physician if:

You experience prolonged or heavy vaginal bleeding.

The pain is prolonged or severe (lower abdomen and pelvic pain is normal during the first 10–14 days of treatment).

You use oral contraception or barrier contraceptive methods.

About 4%–5% of women experience unsuccessful *methotrexate* treatment and require surgery.

hCG, human chorionic gonadotropin; SGOT, serum glutamic-oxaloacetic transaminase; BUN, blood urea nitrogen; CBC, complete blood count; WBC, white blood cell; PO, by mouth; bid, twice daily.

Patient Follow-Up

After intramuscular administration of *methotrexate*, patients are monitored on an outpatient basis. Patients who report severe pain or pain that is prolonged are evaluated by measuring hematocrit levels and performing transvaginal ultrasonography. The ultrasonography findings during follow-up, although usually

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not helpful, can be used to provide reassurance that the tube has not ruptured (161). Cul-de-sac fluid is a common finding, and the amount of fluid may increase if a tubal abortion occurs. It usually is not necessary to intervene surgically, however, unless the patient has a precipitous drop in hematocrit levels or she becomes hemodynamically unstable.

Patients are asked not to become pregnant for at least 2 months after treatment. Hysterosalpingography can be performed, although the procedure is not mandatory.

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Candidates for Methotrexate

To maximize the safety of treatment and to eliminate the possibility of treating in the presence of a nonviable or early viable intrauterine pregnancy, patients considered candidates for *methotrexate* treatment should include those to whom the following factors apply:

- An hCG level is present after salpingostomy or salpingotomy.
- The hCG level is rising or reached a plateau at least 12 to 24 hours after suction curettage.
- No intrauterine gestational sac or fluid collection is detected by transvaginal ultrasonography, the hCG level is greater than 2,000 mIU/mL, the hCG level is rising, and an ectopic pregnancy mass of 4.0 cm or less without cardiac activity or 3.5 cm or less with cardiac activity is visualized.

Ultrasonography findings should be interpreted with caution because most unruptured ectopic pregnancies will be accompanied by fluid in the cul-de-sac.

Side Effects

Opponents of *methotrexate* therapy cite potential side effects as the reason not to use it. Most reported side effects have occurred in patients treated with intravenous *methotrexate* with higher doses and for more prolonged treatment courses than are now required. **When using the single-dose intramuscular regimen, the incidence of side effects is less than 1%, and the failure rate is comparable to that of conservative laparoscopic surgery. One problem that remains puzzling is the inability to predict treatment failures with the use of *methotrexate*. However, the same is true with conservative surgical procedures; thus, the need to monitor hCG levels after salpingostomy or *methotrexate* remains.** In a review of more than 350 women treated with intramuscular *methotrexate*, a high hCG concentration was found to be the most important factor associated with failure of treatment with a single-dose *methotrexate* protocol (162). In patients with an hCG level of less than 10,000 mIU/mL, the overall success rate was 93.4%, as compared with 60.7% when the hCG level was greater than 10,000 mIU/mL. Although surgical management of ectopic pregnancy remains the mainstay of treatment worldwide, *methotrexate* treatment is appropriate in select patient populations.

Reproductive Function

Although there are few data, reproductive function after *methotrexate* treatment can be assessed on the basis of tubal patency and pregnancy outcome. Tubal patency is reported to be 50% to 100%, with a mean of 71%, after systemic *methotrexate* treatment. In two separate reports of 23 and 62 patients, the tubal patency rates on the ipsilateral side were 81.4% and 82.3%, respectively (156,163).

Pregnancy outcome after *methotrexate* administration was reported in a group of 14 patients who attempted pregnancy after receiving multiple intramuscular doses. Of these 14 women, 11 (78.6%) became pregnant; 10 of 11 (90.9%) were intrauterine pregnancies, and one (9%) was an extrauterine pregnancy (156). The mean time from first attempting to achieving pregnancy was 2.3 months (range, 1 to 4 months). In another study of 49 patients who were attempting pregnancy after completion of single-dose intramuscular *methotrexate* administration, 39 (80%) became pregnant; 34 (87%) were intrauterine pregnancies, and 5 (13%) were ectopic pregnancies (164). The mean time from attempting to achieving pregnancy was 3.2 ± 1.1 months. In 87 pregnancies after *methotrexate* therapy, the combined intrauterine pregnancy rate was 86%, and the ectopic pregnancy rate was 14%.

In a combined series of 527 patients treated by laparoscopic linear salpingostomy or salpingotomy, the intrauterine pregnancy rate was 54%, and the recurrent ectopic pregnancy rate was 13% (165). **Comparison of laparoscopically treated patients with**

***methotrexate*-treated patients suggests that the two methods have similar reproductive outcomes.**

Other Drugs and Techniques

Salpingocentesis is a technique in which agents such as KCl, *methotrexate*, prostaglandins, and hyperosmolar glucose are injected into the ectopic pregnancy transvaginally using ultrasonographic guidance, transcervical tubal cannulization, or laparoscopy. Agents injected under ultrasonographic guidance have included *methotrexate* (166,167,168,169,170), KCl (171), combined *methotrexate* and KCl (172), and *prostaglandin E₂* (173). The potential advantages of salpingocentesis include a one-time injection with the potential avoidance of systemic side effects. Reproductive function after this form of treatment has not been reported. Because of the limited experience, this treatment cannot be recommended until there is further study.

Agents injected into the amniotic sac at laparoscopy have included *prostaglandin F_{2a}* (174), hyperosmolar glucose (175), and *methotrexate* (176). This method has the obvious disadvantage of requiring laparoscopy, but it can be used if laparoscopy has been performed. Other agents reported for the treatment of ectopic pregnancy include *RU-486* (177) and anti-hCG antibody (178).

Types of Ectopic Pregnancy

Spontaneous Resolution

Some ectopic pregnancies resolve by resorption or by tubal abortion, obviating the need for medical or surgical therapy (179,180,181,182,183). The proportion of ectopic pregnancies that resolve spontaneously and the reason they do so while others do not are unknown. There are no specific criteria for patient selection that predict successful outcome after spontaneous resolution. A falling hCG level is the most common indicator used, but tubal rupture can occur even with falling hCG levels.

Persistent Trophoblastic Tissue

Persistent ectopic pregnancy occurs when a patient has undergone conservative surgery (e.g., salpingostomy, fimbrial expression) and viable trophoblastic tissue remains. Histologically, there is no identifiable embryo, the implantation usually is medial to the previous tubal incision, and residual chorionic villi usually are confined to the tubal muscularis. Peritoneal trophoblastic tissue implants may also be responsible for persistence (184,185,186,187,188,189).

The incidence of persistent ectopic pregnancy has increased with the increased use of surgery that conserves the tubes. Persistence is diagnosed when the hCG levels plateau after conservative surgery. Persistent ectopic gestation is best diagnosed by an initial measurement of serum hCG or progesterone levels 6 days postoperatively and at 3-day intervals thereafter (187). Risk factors for persistent ectopic pregnancy are based on the type of surgical procedure, the initial hCG level, the duration of amenorrhea, and the size of the ectopic pregnancy. **A slower decline of serum hCG levels has been seen in patients treated by salpingostomy compared with patients treated by salpingectomy. The incidence of persistence after laparoscopic linear salpingostomy ranges from 3% to**

20% (190,191). It is uncertain whether the incidence of persistent ectopic pregnancy is the same or greater when the procedure is performed by laparoscopy versus laparotomy. In a review of medical records from 157 patients who underwent salpingostomy for intact ampullary ectopic pregnancy, 16 of 103 patients (16%) undergoing laparoscopic salpingostomy were treated for persistent ectopic pregnancy, whereas 1 of 54 women (2%) who had salpingostomy by laparotomy was treated for persistent ectopic pregnancy (185). In one study, 23% of women with a preoperative hCG level of less than 3,000 mIU/mL developed persistent ectopic pregnancy, whereas persistent ectopic pregnancy occurred in only 1 of 67 women with a level of more than 3,000 mIU/mL (188). It also was noted that 36% of women with an hCG level of more than 1,000 mIU/mL on the second postoperative day and 64% of

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patients with an hCG level of more than 1,000 mIU/mL on the seventh postoperative day developed persistence. Amenorrhea of less than 7 weeks' duration and ectopic mass smaller than 2 cm have also been reported to increase the risk of persistent ectopic pregnancy (186,188).

Persistent ectopic pregnancy can be treated surgically or medically; surgical therapy consists of either repeat salpingostomy or, more commonly, salpingectomy. Methotrexate offers an alternative to patients who are hemodynamically stable at the time of diagnosis. Methotrexate may be the treatment of choice because the persistent trophoblastic tissue may not be confined to the tube and, therefore, not readily identifiable during repeat surgical exploration (191,192,193).

Chronic Ectopic Pregnancy

Chronic ectopic pregnancy is a condition in which the pregnancy does not completely resorb during expectant management. The condition arises when there is persistence of the chorionic villi with bleeding into the tubal wall, which is distended slowly and does not rupture. It may also arise from chronic bleeding from the fimbriated end of the fallopian tube with subsequent tamponade. In a series of 50 patients with a chronic ectopic pregnancy, pain was present in 86%, vaginal bleeding was present in 68%, and both symptoms were present in 58% (194). Ninety percent of the patients had amenorrhea ranging from 5 to 16 weeks (mean, 9.6 weeks). Most patients develop a pelvic mass that usually is symptomatic. The hCG level usually is low but may be absent; ultrasonography may be helpful in the diagnosis; rarely, bowel involvement or ureteral compression or obstruction exists (194,195).

This condition is treated surgically with removal of the affected tube. Often, the ovary must be removed because there is inflammation with subsequent adhesion development. A hematoma may be present secondary to chronic bleeding.

Nontubal Ectopic Pregnancy

Cervical Pregnancy

The incidence of cervical pregnancy in the United States ranges from 1 in 2,400 to 1 in 50,000 pregnancies (196). A variety of conditions are thought to predispose to the development of a cervical pregnancy, including previous therapeutic abortion, Asherman's syndrome, previous cesarean delivery, *diethylstilbestrol* exposure, leiomyomas, and IVF (196,197,198).

The diagnostic criteria for cervical pregnancy were established based on histologic analysis of a hysterectomy specimen (196). Clinical criteria include the following findings (198):

The uterus is smaller than the surrounding distended cervix.

- The internal os is not dilated.
- Curettage of the endometrial cavity is nonproductive of placental tissue.
- The external os opens earlier than in spontaneous abortion.

Ultrasonographic diagnostic criteria have also been described that are helpful in differentiating a true cervical pregnancy from an ongoing spontaneous abortion (Table 18.5). Magnetic resonance imaging of the pelvis has also been used in this situation (199). Other potential diagnoses that must be differentiated from cervical pregnancy include cervical carcinoma, cervical or prolapsed submucous leiomyomas, trophoblastic tumor, placenta previa, and low-lying placenta.

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Table 18.5 Ultrasound Criteria for Cervical Pregnancy

1. Echo-free uterine cavity or the presence of a false gestational sac only
2. Decidual transformation of the endometrium with dense echo structure
3. Diffuse uterine wall structure
4. Hourglass uterine shape
5. Ballooned cervical canal
6. Gestational sac in the endocervix
7. Placental tissue in the cervical canal
8. Closed internal os

From **Hofmann HMH, Urdl W, Hofler H, et al.** Cervical pregnancy: case reports and current concepts in diagnosis and treatment. *Arch Gynecol Obstet* 1987;241:63–69, with permission.

When a cervical pregnancy is diagnosed before surgery, the preoperative preparation should include blood typing and cross-matching, establishment of intravenous access, and detailed informed consent. This consent should include the possibility of hemorrhage that may require transfusion or hysterectomy.

Nonsurgical treatment, including intraamniotic and systemic *methotrexate* administration, has been used successfully (200,201).

The diagnosis may not be suspected until the patient is undergoing suction curettage for a presumed incomplete abortion and hemorrhage occurs. In some cases, bleeding is light, whereas in others, there is hemorrhage. **Various techniques that can be used to control bleeding include uterine packing, lateral cervical suture placement to ligate the lateral cervical vessels, placement of a cerclage, and insertion of an intracervical 30-mL Foley catheter in an attempt to tamponade the bleeding. Alternatively, angiographic artery embolization can be used. If laparotomy is required, an attempt can be made to ligate the uterine or internal iliac arteries (202,203,204). When none of these methods is successful, hysterectomy is required.**

Ovarian Pregnancy

A pregnancy confined to the ovary represents 0.5% to 1% of all ectopic pregnancies

and is the most common type of nontubal ectopic pregnancy. The incidence ranges from 1 in 40,000 to 1 in 7,000 deliveries (205,206). The diagnostic criteria were described in 1878 by Spiegelberg (Table 18.6). Unlike tubal gestation, ovarian pregnancy is associated with neither PID nor infertility. The only risk factor associated with the development of an ovarian pregnancy is the current use of an intrauterine device.

Table 18.6 Criteria for Ovarian Pregnancy Diagnosis

1. The fallopian tube on the affected side must be intact.
2. The fetal sac must occupy the position of the ovary.
3. The ovary must be connected to the uterus by the ovarian ligament.
4. Ovarian tissue must be located in the sac wall.

From **Spiegelberg O.** Casusistik der ovarialschwangerschaft. *Arch Gynaecol* 1878;13:73.

Patients have symptoms similar to those of ectopic pregnancies in other sites. Misdiagnosis is common because it is confused with a ruptured corpus luteum in up to 75% of cases (205). As with other types of ectopic pregnancy, an ovarian pregnancy has also been reported after hysterectomy (207). Ultrasonography has made preoperative diagnosis possible in some cases (208).

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The treatment of ovarian pregnancy has changed. Whereas oophorectomy had been advocated in the past, **ovarian cystectomy has become the preferred treatment** (209). It is possible to perform cystectomy using laparoscopic techniques (210,211). Treatment with *methotrexate* or *prostaglandin* injection has also been reported (211).

Abdominal Pregnancy

Abdominal pregnancies are classified as primary and secondary. Listed in Table 18.7 are criteria for classifying a primary abdominal pregnancy. Secondary abdominal pregnancies are by far the most common and result from tubal abortion or rupture or, less often, from subsequent implantation within the abdomen after uterine rupture. The incidence of abdominal pregnancy varies from 1 in 372 to 1 in 9,714 live births (212). **Abdominal pregnancy is associated with high morbidity and mortality, with the risk for death 7 to 8 times greater than from tubal ectopic pregnancy and 90 times greater than from intrauterine pregnancy.** There are scattered reports of term abdominal pregnancies. When this occurs, perinatal morbidity and mortality are high, usually as a result of growth restriction and congenital anomalies such as fetal pulmonary hypoplasia, pressure deformities, and facial and limb asymmetry. The incidence of congenital anomalies ranges from 20% to 40% (213).

Table 18.7 Studdiford's Criteria for Diagnosis of Primary Abdominal Pregnancy

1. Presence of normal tubes and ovaries with no evidence of recent or past pregnancy
2. No evidence of uteroplacental fistula
3. The presence of a pregnancy related exclusively to the peritoneal surface and early enough to eliminate the possibility of secondary implantation after primary tubal nidation

The presentation of patients with an abdominal pregnancy varies and depends on the gestational age. In the first and early second trimester, the symptoms may be the same as with tubal ectopic gestation; in advanced abdominal pregnancy, the clinical presentation is more variable. The patient may report painful fetal movement, fetal movements high in the abdomen, or sudden cessation of movements. Physical examination may disclose persistent abnormal fetal positioning, abdominal tenderness, a displaced uterine cervix, easy palpation of fetal parts, and palpation of the uterus separate from the gestation. The diagnosis may be suspected when there are no uterine contractions after *oxytocin* infusion. Other diagnostic aids include abdominal radiography, abdominal ultrasonography, computed tomography scanning, and magnetic resonance imaging (214,215).

Because the pregnancy can continue to term, the potential maternal morbidity and mortality are very high. As a result, **surgical intervention is recommended when an abdominal pregnancy is diagnosed**. At surgery, the placenta can be removed if its vascular supply can be identified and ligated, but hemorrhage can occur, requiring abdominal packing that is left in place and removed after 24 to 48 hours. Angiographic arterial embolization has been described (216). If the vascular supply cannot be identified, the cord is ligated near the placental base, and the placenta is left in place. Placental involution can be monitored using serial ultrasonography and assessment of hCG levels. Potential complications of leaving the placenta in place include bowel obstruction, fistula formation, and sepsis as the tissue degenerates. *Methotrexate* treatment appears to be contraindicated because of a high rate of complications, including sepsis and death, believed to be a result of rapid tissue necrosis (217).

Interstitial Pregnancy

Interstitial pregnancies represent about 1% of ectopic pregnancies. These patients tend to present later in gestation than those with tubal pregnancies. Interstitial pregnancies often are associated with uterine rupture; therefore, they represent a disproportionately large percentage of fatalities from ectopic pregnancy. Treatment is

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cornual resection by laparotomy, although laparoscopic management has also been described (218).

Interligamentous Pregnancy

Interligamentous pregnancy is a rare form of ectopic pregnancy that occurs in about 1 in every 300 ectopic pregnancies (219). An interligamentous pregnancy usually results from trophoblastic penetration of a tubal pregnancy through the tubal serosa and into the mesosalpinx, with secondary implantation between the leaves of the broad ligament. It can

also occur if a uterine fistula develops between the endometrial cavity and the retroperitoneal space. As in abdominal pregnancy, with interligamentous pregnancy the placenta may be adherent to the uterus, bladder, and pelvic side walls. If possible, the placenta should be removed; when this is not possible, it can be left *in situ* and allowed to resorb. Cases of live birth have been reported with this type ectopic gestation (219).

Heterotopic Pregnancy

Heterotopic pregnancy occurs when intrauterine and ectopic pregnancies coexist.

The reported incidence varies widely from 1 in 100 to 1 in 30,000 pregnancies

(220). Patients who have undergone ovulation induction have a much higher incidence of heterotopic pregnancy than those who have a spontaneous conception. An intrauterine pregnancy is seen during ultrasonography examination, and an extrauterine pregnancy may be overlooked easily. Serial hCG levels often are not helpful because the intrauterine pregnancy causes the hCG level to rise appropriately.

The ectopic pregnancy is treated surgically; once the ectopic pregnancy has been removed, intrauterine pregnancy continues in most patients. It may be possible to treat the ectopic pregnancy using nonchemotherapeutic medical treatment, such as KCl, by transvaginal or laparoscopically directed injection.

Multiple Ectopic Pregnancies

Twin or multiple ectopic gestations occur less frequently than heterotopic gestations and may appear in a variety of locations and combinations. About 250 twin ectopic gestations have been reported

(221). Although most reports are confined to twin tubal gestations, ovarian, interstitial, and abdominal twin pregnancies have been reported. Twin and triplet gestations have been reported following partial salpingectomy (222) and IVF (223). Management is similar to that of other types of ectopic pregnancy and is somewhat dependent on the location of the pregnancy.

Pregnancy After Hysterectomy

The most unusual form of ectopic pregnancy is one that occurs after vaginal or abdominal hysterectomy (224,225). Such a pregnancy may occur after supracervical hysterectomy because the patient has a cervical canal that may provide intraperitoneal access. Pregnancy may occur in the perioperative period with implantation of the fertilized ovum in the fallopian tube. Pregnancy after total hysterectomy probably occurs secondary to a vaginal mucosal defect that allows sperm into the abdominal cavity.

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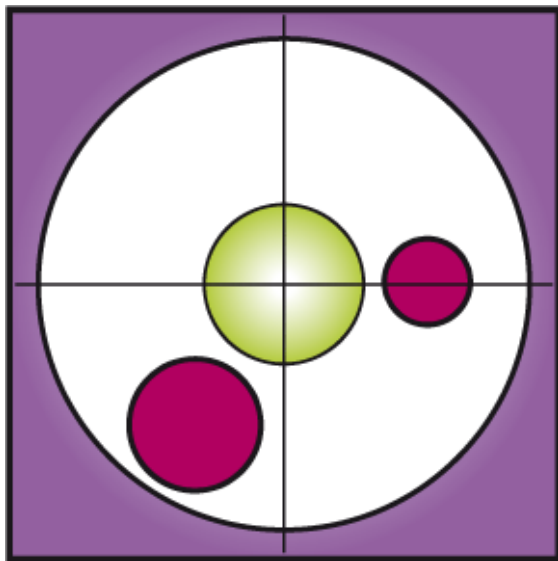
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19

Benign Breast Disease

Baiba J. Grube

Armando E. Giuliano



- **Early detection of breast cancer is improved by risk assessment, clinical breast examination, and screening mammography.**
- **Triple-test concordance requires agreement between results of clinical breast examination, breast imaging, and tissue diagnosis. In the absence of concordance, further diagnostic intervention is required.**
- **The most common benign breast problems include fibrocystic changes and mastalgia. These problems are usually best treated by reassurance. Pharmaceutical agents are available but have side effects that usually are not well tolerated.**
- **Histologic differences exist between fibroadenomas and phyllodes tumors; phyllodes tumors require excision, whereas small asymptomatic fibroadenomas can be observed if the diagnosis is confirmed by histologic or cytologic assessment and there is no evidence of growth.**
-

Spontaneous, unilateral, bloody discharge requires histologic evaluation to exclude malignancy, but symptoms usually are caused by a benign process such as intraductal papilloma or duct ectasia.

- **Breast abscesses are managed with fine needle aspiration and antibiotics, with use of incision and drainage reserved for recurrence.**

Practicing gynecologists should be familiar with techniques for the diagnosis and management of common benign breast conditions, particularly those that mimic malignancy, as well as options for their treatment (1). Benign breast disease is a complex entity of its own with a range of physiologic changes and clinical manifestations that have an impact on a woman's health independent of breast cancer risk (2).

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Detection

History

Evaluation of a new breast symptom begins with assessment of symptoms based on a thorough clinical history (3). The history should include questions regarding current symptoms, duration of the condition, fluctuation of the signs and symptoms, and factors that aggravate or relieve the symptom. **Assessment of breast problems should focus on the following points:**

- Nipple discharge
- Characteristics of discharge (spontaneous or nonspontaneous, appearance, unilateral or bilateral, single or multiple duct involvement)
- Breast mass (size and change in size, density, or texture)
- Breast pain (cyclic versus continuous)
- Association of symptoms with menstrual cycle
- Change in breast shape, size, or texture
- Previous breast biopsies

The patient should be questioned about the following risk factors for breast cancer (see Chapter 38 for more details).

- Sex

- Increasing age (approximately 50% of breast cancers occur *after* age 65)
- Age of menarche less than 12 years
- Nulliparity or first pregnancy at greater than 30 years of age
- Late menopause (older than 55 years of age)
- Family history of breast cancer (especially premenopausal or bilateral disease)
- Number of first-degree relatives with breast cancer and their ages when diagnosed
- Family history of male breast cancer
- Inherited conditions associated with a high risk for breast cancer, including *BRCA1* and *BRCA2* genes, Li-Fraumeni syndrome, Cowden's disease, ataxia telangiectasia syndrome, and Peutz-Jeghers syndrome
- Other malignancies (ovary, colon, and prostate)
- Pathology of previous breast biopsy showing atypia or lobular or ductal carcinoma in situ
- Hormone therapy
- Alcohol consumption
- Postmenopausal weight gain
- Personal history of breast cancer

Breast cancer risk can be determined by the **Gail Risk assessment model**, which is available electronically (4). **The Gail Risk assessment model calculates risk based on patient race, age, age of menarche, age of first live birth, number of first-degree relatives with breast cancer, number of previous breast biopsies, and presence of atypia on the biopsy.**

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It also is important to obtain a current list of medications used, including hormone therapy and herbal medications such as phytoestrogens. The gestational history should take into consideration the possibility that the patient may be pregnant. A personal history of exposure to radiation, especially in the treatment of childhood malignancies, is associated with a higher incidence of developing breast cancer (5). The goal of breast evaluation is to determine clearly if the symptom represents a benign breast condition or may be indicative of a neoplastic process.

Physical Examination

Breast tumors, particularly cancerous ones, usually are asymptomatic and are discovered only by physical examination or screening mammography. Typically, the breast changes slightly during the menstrual cycle. During the premenstrual phase, most women have increased innocuous nodularity and mild engorgement of the breast. Rarely, these characteristics can obscure an underlying lesion and make examination difficult. Findings should be carefully documented in the medical record to serve as a baseline for future reference.

Inspection

Inspection is performed initially while the patient is seated comfortably with her arms relaxed at her sides. The breasts are compared for symmetry, contour, and skin appearance. Edema or erythema is identified easily, and skin dimpling or nipple retraction is shown by having the patient raise her arms above her head and then press her hands on her hips, thereby contracting the pectoralis muscles (Fig. 19.1). Palpable and even nonpalpable tumors that distort Cooper's ligaments may lead to skin dimpling with these maneuvers.

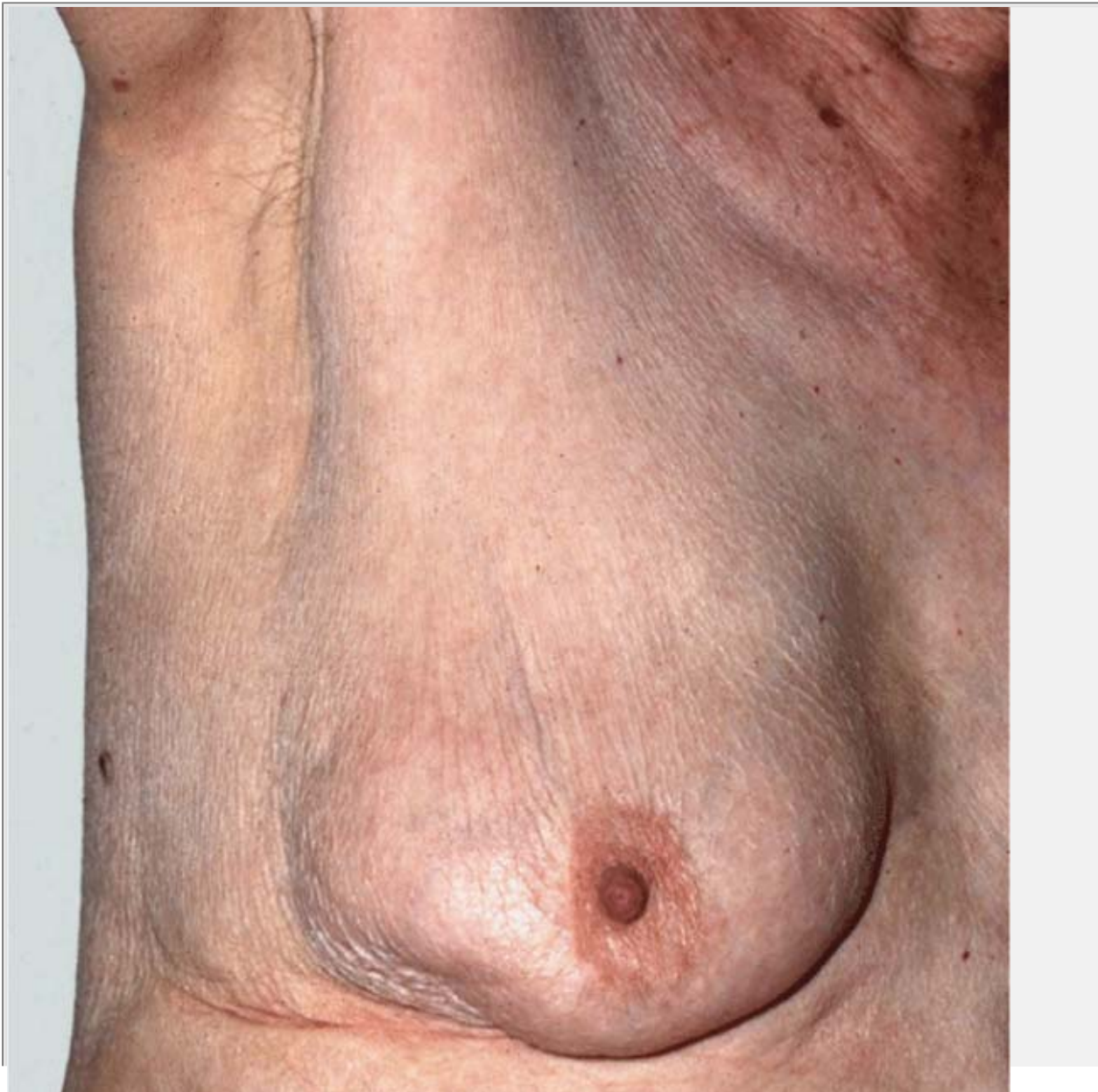




Figure 19.1 Raising the arm reveals retraction of the skin of the lower outer quadrant caused by a small palpable carcinoma. (From Giuliano AE. Breast disease. In: Berek JS, Hacker NF, eds. *Practical gynecologic oncology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005:628, with permission.)

Palpation

While the patient is seated, each breast should be palpated methodically. Some physicians recommend palpating the breast in long strips, but the exact palpation technique used is probably not as important as the thoroughness of its application over the entire breast. One very effective method is to palpate the breast in enlarging concentric circles until the entire breast has been covered. A pendulous breast can be palpated by placing one hand between the breast and the chest wall and gently palpating the breast between both examining hands. The axillary and supraclavicular areas should be palpated for enlarged lymph nodes. The entire axilla, the upper outer quadrant of the breast, and the axillary tail of Spence are palpated for possible masses.

While the patient is supine with one arm over her head, the ipsilateral breast is again methodically palpated from the clavicle to the costal margin. If the breast is large, a pillow or towel should be placed beneath the scapula to elevate the side being examined; otherwise, the breast tends to fall to the side, making palpation of the lateral hemisphere more difficult. The major features to be identified on palpation of the breast are temperature, texture and thickness of skin, generalized or focal tenderness, nodularity, density, asymmetry, dominant masses, and nipple discharge. Most premenopausal patients have normally nodular breast parenchyma. The nodularity is diffuse but predominantly in the upper outer quadrants, where there is more breast tissue. These benign parenchymal nodules are small, similar in size, and indistinct. By comparison, breast cancer usually occurs in the form of a nontender, firm mass with irregular margins. A cancerous mass feels distinctly different from the surrounding nodularity. A malignant mass may be fixed to the skin or to the underlying fascia. A suspicious mass is usually unilateral. Similar findings in both breasts are unlikely to represent malignant disease (6).

Breast Self-examination

Breast self examination (BSE) increases breast health awareness (7,8). It helps promote early detection of cancer and may improve the survival rates for patients with breast carcinoma (9,10,11). Most breast cancers are detected by women themselves (48%), followed by breast imaging (41%), and by physician clinical examination in only 11%

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(12). Although young women have a low incidence of breast cancer, it is important to teach self-examination early so that it becomes habitual. Organizations such as the American Cancer Society sponsor courses in BSE. Reassurance, support, and patient education may encourage women to overcome psychologic barriers to routine BSE (13). Such instruction also available is through electronic resources (14).

The following seven "P's represent essential components of breast examination:

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Positions

- Palpation
- Pads of fingers for palpation

Pressure

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- Perimeter
- Pattern of search
- Patient education

The woman should inspect her breasts while standing or sitting before a mirror, looking for any asymmetry, skin dimpling, or nipple retraction. Elevating her arms over her head or pressing her hands against her hips to contract the pectoralis muscles will highlight any skin dimpling. Finally, the woman should examine her breasts while bending over and leaning forward. While standing or sitting, she should carefully palpate her breasts with the fingers of the opposite hand. She should then lie down and again palpate each quadrant of the breast as well as the axilla using the pads of the three middle fingers with three pressures—light, medium, and deep—covering the entire breast from the clavicle to the inframammary fold, from sternum to latissimus dorsi laterally. The area within the perimeter of the breast should be palpated, preferably using an up-and-down method called vertical stripe, rather than the concentric circular or radial methods, in which the edges of the breast tissue often are omitted. Many women feel anxious about performing breast examination. The examination may be performed while showering; soap and water may increase the sensitivity of palpation, and the privacy of the shower may provide a less anxiety-provoking environment.

It is helpful for all women to examine their breasts at the same time each month to develop a routine. Premenopausal women should examine their breasts monthly 7 to 10 days after the onset of the menstrual cycle. For postmenopausal women, selection of a specific calendar date is a helpful way to remember to perform a monthly BSE.

Women should be instructed to report any abnormalities or changes to their physicians. If the physician cannot confirm the patient's findings, the examination should be repeated in 1 month or after her next menstrual period.

Breast Imaging

Mammography

The best method for imaging of the breast is screen-film mammography (15). Full-field digital mammography, which records mammographic images on a computer, is a modification of screen-film mammography (16). Some advantages of digital mammography include lower radiation exposure, ability to manipulate a computerized image for optimal viewing, and access to distance consultations through telemammography (17). Studies comparing the sensitivity of full-field digital mammography with screen-film mammography

in detecting cancer have had mixed results. Full-field digital mammography had lower detection rates than screen-film mammography in community-based programs, but a randomized trial showed full-field digital mammography to have higher detection rates and lower recall rates than screen-film mammography (16,18).

Slow-growing breast cancers can be identified by mammography at least 2 years before the mass reaches a size detectable by palpation. These tumors have a less aggressive biologic behavior than interval breast cancers (19,20,21). In fact, mammography is the only reproducible method of detecting nonpalpable breast cancer, but its use depends on the availability of state-of-the-art equipment and a dedicated breast radiologist.

Compression of the breast is necessary to obtain good images, and patients should be forewarned that breast compression is uncomfortable. With good technique and well-maintained modern equipment, exposure to radiation can be limited. For all facilities in the United States inspected under the Mammography Quality Standards Act in the first

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one half of 1997, the average mean glandular radiation dose per mammographic image was 1.6 mGy (160 mrad) (22).

Indications for Mammography

The indications for mammography are as follows:

- **To screen, at regular intervals, women who are at high risk for developing breast cancer.** About one third of the abnormalities detected on screening mammography prove malignant when biopsy is performed (23).
- **To evaluate a questionable or ill-defined breast mass or other suspicious change in the breast that is detected by clinical breast examination.**
- **To establish a baseline breast mammogram and reevaluate patients at yearly intervals to diagnose a potentially curable breast cancer before it has been diagnosed clinically.**
- **To search for occult breast cancer in a patient with metastatic disease in axillary nodes or elsewhere from an unknown primary origin.**
- **To screen for unsuspected cancer before cosmetic operations or biopsy of a mass.**
- **To monitor breast cancer patients who have been treated with a breast-conserving surgery and radiation.**

Screening

Screening programs to evaluate asymptomatic, healthy women combine physical examination with mammographic screening to identify breast abnormalities. During the past 30 years, there has been an increase in the use of mammography, mammographic screening, and public awareness of breast health care. The cancer detection rate for screening mammography is 5 per 1,000 screening examinations (24). The cancer detection rate is 11-fold higher, at 55 per

1,000 examinations, when breast imaging is performed for a specific finding (i.e., diagnostic imaging) (24). Of seven randomized mammographic screening trials performed, five have demonstrated a reduction in overall mortality from breast cancer screening programs (25,26,27,28,29,30,31,32). A study from the Rhode Island Cancer Registry indicates that the institution of population-based breast cancer screening programs can result in the reduction in the median tumor size at initial detection from 2.0 to 1.5 cm, which is associated with a 25% reduction in mortality (33). Detecting breast cancer before it has spread to the axillary nodes greatly increases the chance of survival; about 85% of women with such cancer will survive at least 5 years (31,34). Because breast cancer presents first as local disease, screening mammography for breast cancer in asymptomatic women can detect small tumors that have a better prognosis. These tumors have not had the opportunity to metastasize regionally or systemically; thus women have more options for treatment with reduced toxicity.

The American Cancer Society has published an extensive review of the benefits, limitations, and potential harms of screening mammography (35). In addition, it addresses the role of physical examination, discusses screening in older and high-risk women, and reviews the role of newer technologies. **A summary of the guidelines recommends that women of average risk for breast cancer begin mammographic screening at age 40. The rationale for beginning mammographic screening at age 40 is a 24% reduction in mortality in screened populations** (28). For women in their 20s and 30s, a clinical breast examination is suggested at least every 3 years, and preferably annually, as part of a well-woman examination. For women older than age 40 years, annual clinical breast

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examination and mammography are recommended. For older women, recommendations for mammographic screening may be individualized based on the presence of any comorbidities. Chronologic age alone should not be considered a contraindication to mammographic screening as long as a woman is in reasonable health and has a life expectancy of 3 to 5 years (35). **The American Geriatrics Society recommends annual or at least biennial mammography for women up to age 75 years, and after that age, every 2 to 3 years if the woman has a life expectancy of more than 4 years** (36). The reasons for liberalization of the screening interval recommendations for older women include improved biology profile, slower growth rate, and lower risk for recurrence (37,38,39,40,41). The natural history of the disease in older women must be balanced against life expectancy as a function of overall health (42). **For high-risk women, consideration can be given to earlier initiation of screening (5–10 years earlier than the age of the index case) and shorter intervals between screening**, as well as the use of additional imaging modalities such as breast ultrasonography and magnetic resonance imaging (MRI) with dedicated breast coils. No screening test is perfect, however, and false-negative imaging studies or benign clinical examinations may lead the patient to an erroneous sense of well-being only to be confronted later with a subsequent interval cancer. Likewise, a false-positive result can lead to significant anxiety and unnecessary biopsy.

Mammographic Abnormalities

A mammographic abnormality includes a mass (solid versus cystic), microcalcifications (benign, indeterminate, suspicious), asymmetric density, architectural distortion, and appearance of a new density. There are eight morphologic categories of mammographic abnormalities (43,44):

- Calcification distribution

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Number of calcifications

- Description of calcifications
- Mass margin
- Shape of mass
- Density of mass
- Associated findings
- Special cases

Mammographic abnormalities should be visible on two views, usually craniocaudal (CC) and mediolateral oblique (MLO). The lesion should triangulate to the same location on those two views. Calcifications can be macrocalcifications, which are coarse and usually represent benign degenerative breast conditions. Calcifications associated with breast cancer are clustered pleomorphic microcalcifications; typically, five to eight or more calcifications are aggregated in one part of the breast (45). These calcifications may be associated with a mammographic mass density. A mass density may appear without evidence of calcifications. It can represent a cyst, benign tumor, or a malignancy. A malignant density usually has irregular or ill-defined borders and may lead to architectural distortion, which may be subtle and difficult to detect in a dense breast. Other mammographic findings suggesting breast cancer are architectural distortion, asymmetric density, skin thickening or retraction, or nipple retraction. Examples of mammographic abnormalities can be found in several electronic sources (46).

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Mammographic Reports

The American College of Radiology has recommended the **Breast Imaging Reporting and Data System (BI-RADS)** as a standardized scheme for describing mammographic lesions (47). In the BI-RADS system, there are six categories for mammographic findings (other than incomplete) (43,44).

- Incomplete, needs further imaging
- Negative
- Benign finding
- Probably benign, short-interval follow-up recommended
- Suspicious finding and biopsy should be considered

Highly suggestive of malignancy and appropriate action should be undertaken

- Known malignancy (a category that is often used for follow-up of a lesion that is undergoing neoadjuvant treatment)

The patient should be referred to a surgeon if the report identifies a lesion as a category 4 or 5 (47). A category 0 indicates incomplete evaluation, and further diagnostic studies are required. Category 3 connotes a finding that is most likely benign; a short-interval follow-up is recommended, and breast examination by an expert should be considered.

Correlation of Findings

Biopsy must be performed on patients with a dominant or suspicious mass despite absence of mammographic findings (48). Mammography should be performed before biopsy so other suspicious areas can be noted and the contralateral breast can be checked (Fig. 19.2). **Mammography is never a substitute for biopsy because it may not reveal clinical cancer**, especially when it occurs in the dense breast tissue of young women with fibrocystic changes. In fact, the sensitivity of mammography is 75%, with a specificity of 92.3% depending on the patient's age; breast density; use of hormone therapy; and the size, location, and mammographic appearance of the tumor (49). Mammography is less sensitive in young women with dense breast tissue than in older women, who tend to have fatty breasts, in which mammography can detect at least 90% of malignancies (50). Small tumors, particularly those without calcifications, are more difficult to detect, especially in women with dense breasts.

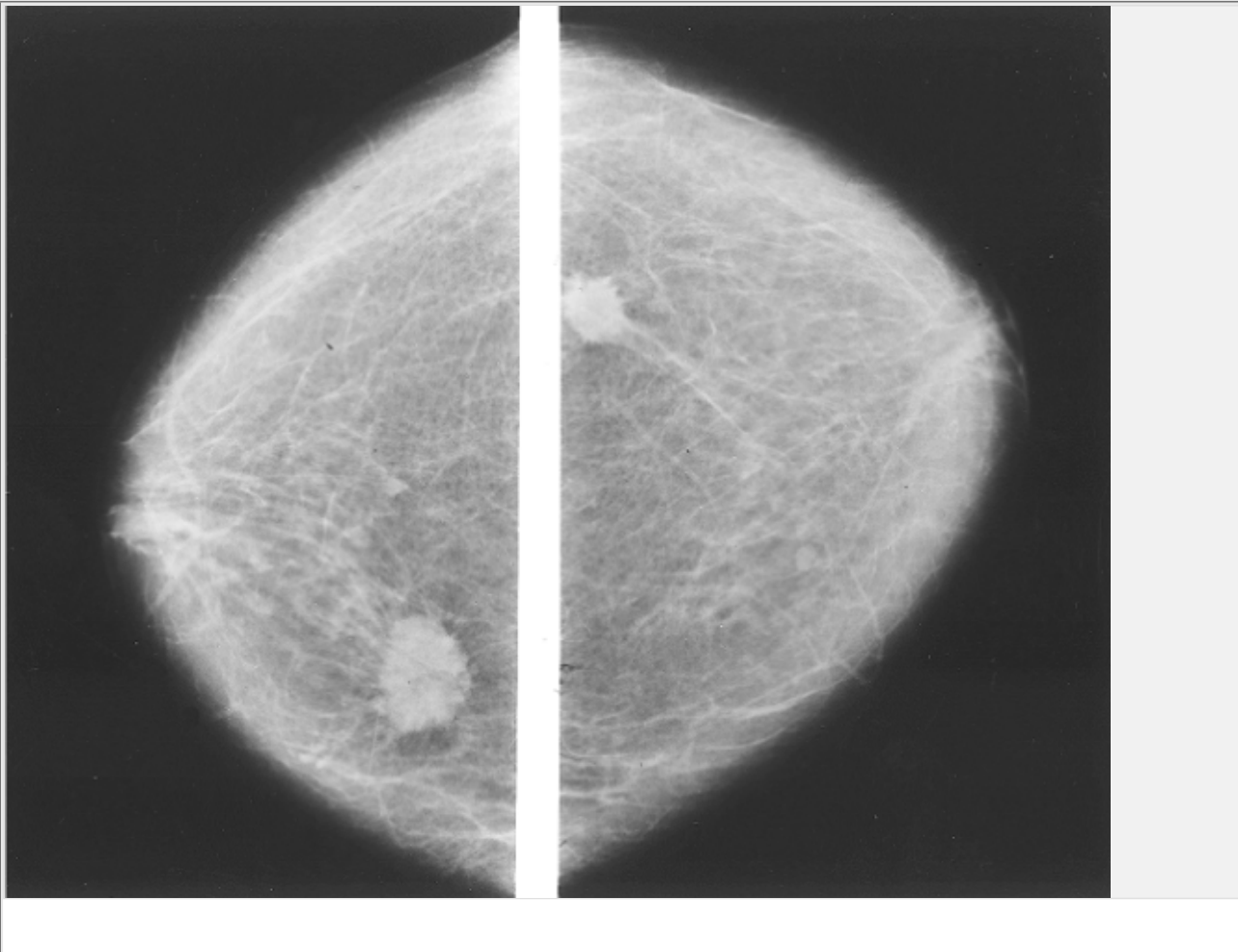


Figure 19.2 Bilateral mammography shows the extent of breast carcinoma, illustrating the importance of bilateral mammography in the workup of a clinically apparent mass. (From Giuliano AE. Breast disease. In: Berek JS, Hacker NF, eds. *Practical gynecologic oncology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005:630, with permission.)

Ultrasonography

Breast ultrasonography is generally used for focused scanning of a questionable finding or for evaluation of a mammographic finding (51). Reliable, portable, computer-enhanced ultrasonography with high-frequency transducers and improved imaging is now available to evaluate and treat problems of the breast (52). It is a sensitive, minimally invasive technique that is being used more frequently in evaluating some breast symptoms, especially in younger women with dense breast tissue, but is dependent on the availability of a skilled ultrasonographer (53). The reporting of findings is not standardized as with the BI-RADS system for mammography. Some lesions can be detected only with ultrasonography (54). It is the preferred modality to distinguish a solid from a cystic mass (52). Breast ultrasonography is not recommended for routine screening, but it has been used to supplement

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mammographic screening in high-risk women (55). Ultrasonography has a higher false-positive rate than mammography (51,53,54).

Following are indications for breast ultrasonography:

- Characterization:
 - Palpable abnormality
 - Ambiguous mammographic findings
 - Silicone leak
 - Mass in woman younger than 30 years, lactating, or pregnant
- Guidance for interventional procedures
- Possible role for additional imaging in high-risk individuals

Ultrasonography is useful in distinguishing benign from malignant lesions if identified by mammography (56). Ultrasonography may be especially useful if the patient feels a mass, but the physician cannot detect an abnormality and the mammogram does not disclose one. It may identify cancers in the dense breast tissue of premenopausal women, but it is usually used to distinguish a benign cyst from a solid tumor. Ultrasonography cannot reliably detect microcalcifications, and it is not as useful as mammography in assessing women with fatty breasts.

Handheld or real-time ultrasonography is 95% to 100% accurate in differentiating solid masses from cysts (57). However, this finding is of limited clinical value because a dominant mass should be evaluated by biopsy, and a cystic mass can be studied by needle aspiration, which is far less expensive than ultrasonography. If such a lesion proves to be a

simple cyst, no further evaluation is necessary. Rarely, ultrasonography may identify a small cancer within a cyst, an intracystic carcinoma. These complex cysts warrant surgical biopsy.

Magnetic Resonance Imaging

Magnetic resonance imaging may be of value in assessing breast lesions of an indeterminate nature detected by clinical and mammographic examination or occurring in patients who have implants (58). Both MRI and positron emission tomography (PET) have been used to identify occult lesions (59,60), and MRI is increasing in popularity as a means of imaging the breast (58,61). It tends to be highly sensitive but not very specific, leading to biopsies of many benign lesions. Image enhancement with gadolinium can discriminate between benign and malignant lesions with varying degrees of accuracy.

Several roles have been proposed for breast MRI. The lack of radiation exposure makes MRI theoretically an ideal method for screening of healthy women, but currently such widespread use is not cost-effective. Focal asymmetry is usually benign but can represent a malignancy. Magnetic resonance imaging may help identify those patients with focal asymmetric areas who should undergo biopsy. Usually, a scar can easily be distinguished from recurrent tumor based on the evaluation and diminution of the scar over time. Some scars, however, do not resolve rapidly and are confused with cancer or, more commonly, with recurrent cancer after breast-conserving surgery and whole breast irradiation. Ideally, such cases are evaluated with MRI, sometimes obviating the need for biopsy. Magnetic resonance imaging is extremely useful in identifying silicone released by ruptured breast implants in patients with augmented breasts (Fig. 19.3). In patients with implants, MRI with gadolinium may be performed to detect breast cancer even if silicone release is not suspected. There may be a role for **MRI in evaluation of specific conditions. It has been used for the following indications:**

- Stage tumor to rule out multicentric disease
- Differentiate postoperative scar from recurrence after breast-conserving surgery
- Find a lesion seen in only one view of mammogram
- Evaluate positive axillary nodes in the presence of negative mammogram and clinical breast examination results
- Rule out silicone implant rupture
- Assess focal asymmetry



Figure 19.3 Mammography shows implant and extracapsular free silicone (arrow).

Potential future considerations for MRI include assessment of *BRCA1* and *2* mutation-carriers, women with personal history of breast cancer, biopsy results showing atypia or local carcinoma *in situ*, young patients, or dense breasts.

A study from the Netherlands in high-risk women reported a 71% sensitivity for MRI compared with 17.9% for clinical breast examination and 40% for mammography (62). The International Cooperative Magnetic Resonance Mammography Study that is currently under way will help identify the advantages and limitations of MRI. At present, MRI should be considered only after conventional imaging is performed; it should not be used as a screening tool or a substitute for mammography or biopsy.

Positive Emission Tomography Scan

Positive emission tomography scanning is a diagnostic modality that assesses the metabolic activity of tumors. Radioactive fluorodeoxyglucose (FDG) is an analog of glucose that is

metabolized by tissues of high metabolic rates. In two prospective trials comparing PET with mammography, primary breast lesions were correctly identified and lymph nodes

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status was determined with a high degree of sensitivity using PET (59,63). This technique has been used to identify occult breast lesions with positive axillary lymph nodes (59).

Breast Tissue Evaluation: Histology and Cytology

The safest course is tissue or cytologic biopsy evaluation of all dominant masses found on physical examination and, in the absence of a mass, of suspicious lesions shown by mammography or ultrasonography. The diagnosis of a benign breast lesion versus breast cancer is often difficult to determine based on clinical examination and ultimately requires evaluation of tissue by fine needle aspiration cytology (FNAC), core needle biopsy (CNB), or excisional biopsy (EB). Both FNAC and CNB are accurate methods of diagnosis when compared with EB and are valuable tools in the assessment of breast lesions (64). The false-positive and false-negative rate for FNAC is 1.7% and 7.1%, and for CNB 0% and 5.7%, respectively (64). Confirmation of the accuracy of a negative FNAC result requires triple-test concordance between breast imaging studies, clinical breast examination, and cytologic assessment. Accuracy can be 100% when all three evaluations have negative results (65). Compared with CNB, FNAC is faster, simpler, and does not require anesthesia. The superiority of FNAC versus CNB has not been established, and the techniques are comparable for

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most lesions. One study reported that FNAC was more sensitive than CNB (97.5% versus 90%, respectively) (66). In recent series comparing CNB with FNAC, the sensitivity was 88% versus 92%, positive predictive value for malignancy was 99% versus 100%, and inadequacy rate 7% versus 7%, respectively (67). The specificity of CNB was found to be higher than that of FNAC (90% versus 82%). Both FNAC and CNB are reasonable techniques for the evaluation of a palpable or image-identified lesion, although FNAC is more accurate when an experienced physician is performing the technique, and it allows immediate assessment of the adequacy of material and additional sampling if there is a paucity of cells (64). Collagenous lesions are more difficult to diagnose by FNAC. Distinguishing invasive from noninvasive carcinoma cannot be done reliably with FNAC. Another technique, imprint cytology from core biopsies, has been used increasingly as an alternative to FNAC.

About 30% of lesions suspected to be cancer prove on biopsy to be benign, and about 15% of lesions believed to be benign prove to be malignant (23). Dominant masses or suspicious nonpalpable mammographic findings must be evaluated by biopsy (48,68). Histologic or cytologic diagnosis should be obtained before the decision is made to monitor a breast mass (69). An exception may be a premenopausal woman with a nonsuspicious mass presumed to be fibrocystic disease. However, **an apparently fibrocystic lesion that does not completely resolve within several menstrual cycles should be sampled for biopsy. Any mass in a postmenopausal woman who is not taking estrogen therapy should be presumed to be malignant.** Some clinicians will monitor a mass when results of the clinical diagnosis, breast imaging studies, and cytologic studies are all in agreement, such as with fibroadenoma. Many clinicians will not leave a dominant mass in the breast even when FNAC results are negative, unless perhaps if the fine-needle aspiration shows fibroadenoma. Such cases require periodic follow-up. Some surgeons excise lesions when the aspiration shows only fibrocystic disease. Presented in Figures 19.4 and 19.5 are algorithms for management of breast masses in premenopausal and postmenopausal patients. Simultaneous evaluation of a breast mass using clinical breast examination, radiography, and FNAC can lower the risk of missing cancer to only 1%, effectively reducing the rate of

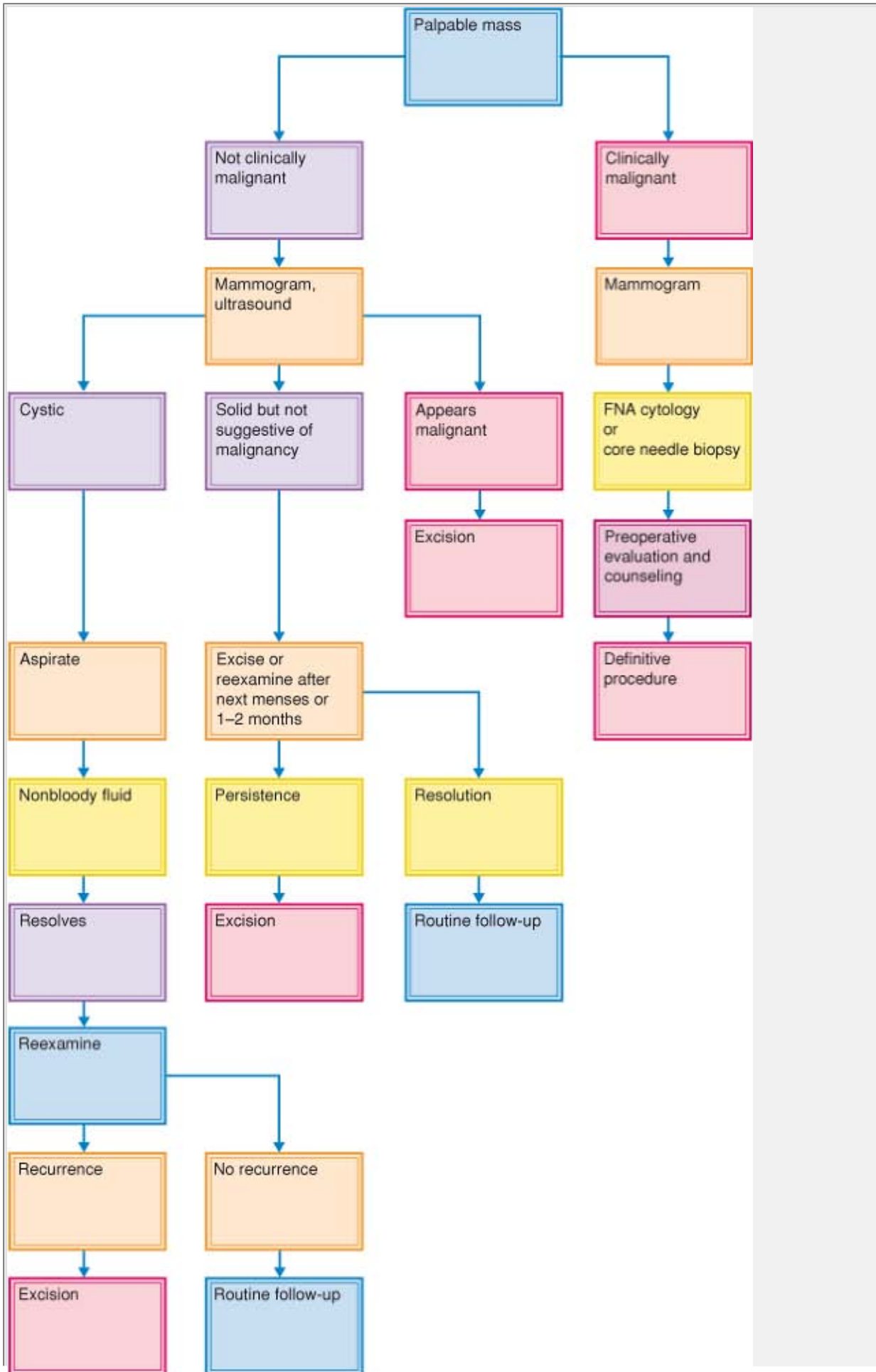


Figure 19.4 Algorithm for management of breast masses in premenopausal women.

(Revised & updated from **Giuliano AE**. Breast disease. In: **Berek JS, Hacker NF**, eds. *Practical gynecologic oncology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005:640, with permission.)

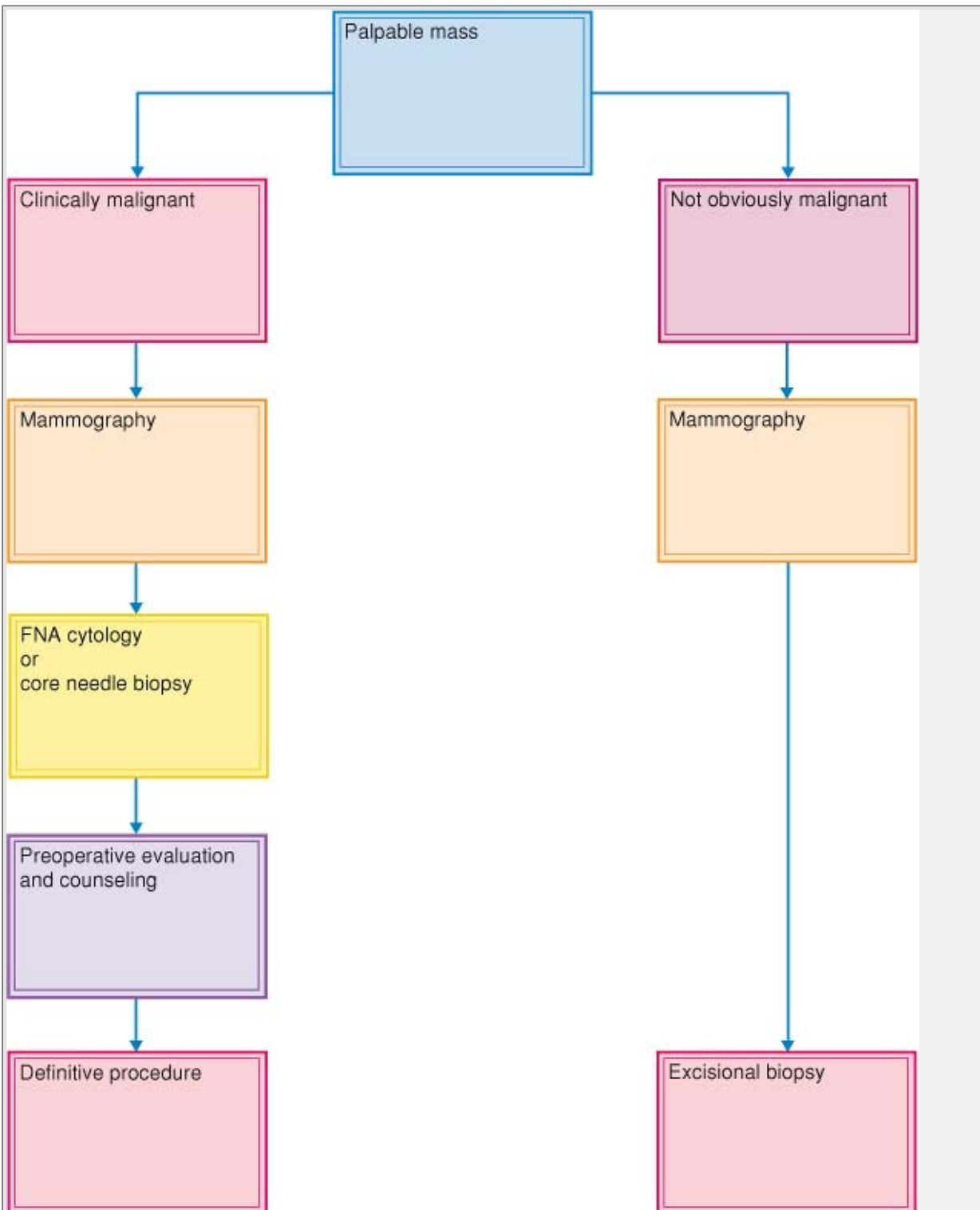


Figure 19.5 Algorithm for management of breast masses in postmenopausal women.

(Revised & updated from **Giuliano AE**. Breast disease. In: **Berek JS, Hacker NF**, eds. *Practical gynecologic oncology*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005:641, with permission.)

If the presence of breast cancer is strongly suggested by physical examination, the diagnosis can be confirmed by FNAC or CNB, and the patient may be counseled regarding treatment. Treatment should not be determined based on results of physical examination and mammography alone, in the absence of biopsy results.

The most reasonable approach to the diagnosis and treatment of breast cancer is outpatient biopsy (either FNAC, CNB, or EB), followed by definitive surgery at a later date if needed. **This two-step approach allows patients to adjust to the diagnosis of cancer, carefully consider alternative forms of therapy, and seek a second opinion. Studies have shown no adverse effect from the 1- to 2-week delay associated with the two-step procedure (71). Because cancer is found in the minority of patients who require biopsy for diagnosis of a breast mass, definitive treatment should not be undertaken without an unequivocal histologic diagnosis of cancer.**

Fine-needle Aspiration

With FNAC, cells from a breast tumor are aspirated with a small (usually 22-gauge) needle and examined by a pathologist. Precise guidelines for this technique are available (72). It can be performed easily, with no morbidity, and is much less expensive than excisional or open biopsy. However, it requires the availability of a pathologist skilled in the cytologic diagnosis of breast cancer to interpret the results, and it is subject to sampling problems, particularly when lesions are deep. Cytologic diagnoses must be correlated with clinical and imaging findings to achieve triple-test concordance and to decrease the false-negative rate (73). **The triple-test concordance (ie, concordance between fine-needle aspiration, physical examination, and mammography) is the foundation of breast evaluation. The triple-test results are more powerful than each modality alone (74).** The incidence of false-positive diagnoses was 0% to 0.3%, and the rate of false-negative diagnoses was 1.4% to 2.3% in several recent studies (74,75).

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Core Needle Biopsy

A core of tissue can be obtained from palpable lesions using a large cutting needle (76). Image-guided large-core needle biopsy is a reliable diagnostic alternative to surgical excision of suspicious nonpalpable breast lesions (77). As in the case of any needle biopsy, the main drawback is false-negative findings caused by improper positioning of the needle. False-negative findings may be reduced if core biopsy is performed with ultrasonographic guidance. **The interpretation of results from CNB is classified by categories B1–B5 (78).**

- B1: Normal tissue
- B2: Benign lesions: fibroadenomas, fibrocystic change, sclerosing adenosis, duct ectasia, fat necrosis, abscess

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- B3: Uncertain malignant potential: atypical epithelial hyperplasia, lobular neoplasia, phyllodes tumor, papillary lesions, radial scar, complex sclerosing lesions

- B4: Suspicious
- B5: Malignant

Open Excisional Biopsy

Open biopsy with local anesthesia as a separate procedure before deciding on definitive treatment is the most reliable means of diagnosis. It is required when the results of needle biopsy are nondiagnostic or equivocal.

Histologic Analysis

Histologic evaluation with hematoxylin and eosin (H&E) staining confirms benign or malignant disease. Images of benign and malignant breast lesions can be viewed through the Internet Pathology Laboratory for Medical Education (79). **Assessment of prognostic factors, tumor grade, estrogen, progesterone, her-2/*neu* receptor status, and proliferative indices is performed on paraffin-fixed tissue by immunohistochemistry (78). Her-2/*neu* assessment in breast cancer by immunohistochemistry (IHC) is appropriate for patients with tumors that score 3+. Fluorescence *in situ* hybridization (FISH) is recommended for 2+ IHC to more accurately assess her-2/*neu* amplification and provide better prognostic information (80).**

Ductal Lavage Cytology

Ductal lavage using a microcatheter is a new modality that has been investigated in high-risk women (81). Patients undergo gentle nipple suction to elicit nipple fluid. A duct that yields fluid is then cannulated with a microcatheter, and 10 to 20 mL of saline are introduced in 2- to 4-mL increments. **The cytologic assessment of a sample obtained by ductal lavage is more sensitive than that of nipple aspiration.** Ductal lavage is a better modality to obtain a large number of cells for cytological evaluation. It is safe and well tolerated (81).

Benign Breast Conditions

Benign breast disorders account for most breast problems. These conditions are frequently considered in the context of excluding breast cancer and often are not recognized for their own associated morbidity (82). To provide appropriate management, it is important to consider benign breast disorders from four aspects: (i) clinical picture, (ii) medical significance, (iii) treatment intervention, (iv) and pathologic etiology (83). A framework to understand benign breast problems is called Aberrations of Normal Development and Involution (ANDI) (2,82,83). It includes symptoms, histology, endocrine state, and pathogenesis in a progression from a normal to a disease state. Most benign breast conditions arise from normal changes in breast development, hormone cycling, and reproductive evolution (82).

Three life cycles reflect different reproductive phases in a woman's life and are associated with unique breast manifestations.

- **During the early reproductive period (15–25 years), lobule and stromal formation occurs.** The ANDI conditions associated with this period are fibroadenoma (mass) and juvenile hypertrophy (excessive breast development). In this first stage, the progression from

ANDI to a disease state results in the formation of giant fibroadenomas and multiple fibroadenomas.

During the mature reproductive period (25–40 years), cyclic hormonal changes affect glandular tissue and stroma. In this second period, the ANDI is an exaggeration of these cyclic effects, such as cyclic mastalgia and generalized nodularity.

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The third phase is involution of lobules and ducts or turnover of epithelia, which occurs during ages 35 to 55 years. The ANDI associated with lobular involution are macrocysts (lumps) and sclerosing lesions (mammographic abnormalities). Those associated with ductal involution are duct dilation (nipple discharge) and periductal fibrosis (nipple retraction), and those with epithelial turnover are mild hyperplasia (pathologic description).

Disease conditions with increased epithelial turnover are epithelial hyperplasias with atypia. Hughes feels that this framework allows the clinician to understand the pathogenesis of these conditions and to understand that these disorders are aberrations of a normal process that does not usually require any specific treatment (82).

Fibrocystic Change

Fibrocystic change, the most common lesion of the breast, is an imprecise term that covers a spectrum of clinical signs and symptoms and histologic changes (76).

The term refers to a histologic picture of fibrosis, cyst formation, and epithelial hyperplasia (83). Cysts arise from the breast lobules and are an aberration of normal breast involution (82). Macroscopic cysts occur in approximately 7% of women, and microscopic, nonpalpable cysts occur in close to 40% of women (84). It is common in women 35 to 55 years of age but rare in postmenopausal women not taking hormone therapy. The presence of estrogen seems necessary for the clinical symptoms to occur. This finding is supported by the observation that it is present bilaterally, increased in the perimenopausal age group, and responsive to endocrine therapy (85). In essence, a diagnosis of fibrocystic change is of little clinical significance as long as malignancy is excluded but can lead to significant patient anxiety (86). These lesions are associated with benign changes in the breast epithelium.

Cyst Fluid Analysis

Investigators have examined the electrolyte and protein content of cyst fluid, but this has been of little significance in the clinical management of fibrocystic disease. The potassium-to-sodium ratio is a marker that may be used to distinguish cyst subtypes (87). Cysts are either lined by apocrine epithelium with a high potassium-to-sodium ratio and a higher hormone or steroid concentration (type I); or by flattened lobule epithelium with a low potassium-to-sodium ratio and a higher concentration of albumin, CEA, CA125, and steroid hormone-binding globulin (type II) (85,87). Apocrine cysts produce and secrete large amounts of prostate-specific antigen (PSA) (88). The role of this serine protease in proliferative breast disease is not fully understood.

Clinical Findings in Fibrocystic Disease

Fibrocystic changes may produce an asymptomatic mass that is smooth and mobile that may be compressible. Fibrocystic change is more often accompanied by pain or tenderness and sometimes nipple discharge. In many cases, discomfort coincides

with the premenstrual phase of the cycle, when the cysts tend to enlarge. Fluctuation in size and rapid appearance or disappearance of a breast mass are common. Multiple or bilateral masses appear frequently, and many patients have a history of a transient mass in the breast or cyclic breast pain. Cyclic breast pain is the most common associated symptom of fibrocystic changes.

Differential Diagnosis

Pain, fluctuation in size, multiplicity of lesions, and bilaterality are the features most helpful to differentiate fibrocystic disease from carcinoma. If a dominant mass is present, however, the diagnosis of cancer should be suspected until it is disproved by complete aspiration of a cyst, or histopathologic analysis if a mass is present after aspiration, or by breast imaging. Microscopic findings associated with fibrocystic disease include cysts (gross and microscopic), papillomatosis, adenosis, fibrosis, and ductal epithelial hyperplasia (89).

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Diagnostic Tests

Patients with cystic disease may have a discrete fibrocystic mass that is frequently indistinguishable from carcinoma based on clinical findings. Mammography may be helpful, but there are no mammographic signs diagnostic of fibrocystic change. Ultrasonography is useful in differentiating a cystic from a solid mass.

Characteristic findings on ultrasonography that confirm a simple cyst include the following:

- Mass with thin walls
- Smooth round shape
- Absence of internal echoes
- Posterior acoustic enhancement

If these imaging criteria are not met, a tissue diagnosis of the mass usually requires a FNA, FNAC, or EB. The finding of a simple cyst by ultrasonography rules out carcinoma. **Any lesion that is suspicious by mammography or ultrasonography should be biopsied.**

When the diagnosis of fibrocystic change has been established by ultrasonography or is practically certain because the history is classic, aspiration of a discrete mass suggestive of a cyst is indicated if the patient is symptomatic, the cyst obscures visualization of breast tissue on mammography and prevents adequate imaging, or if the ultrasonographic criteria are not met. In one study of a screened population, 1% of individuals developed a new cyst that resolved in more than 50% of cases (90). Aspiration may be performed with ultrasonographic guidance, but image guidance is usually not necessary if the cyst is palpable (91). Fine needle aspiration of a cyst is a minimally invasive procedure performed with a 21- or 22-gauge needle without local anesthesia and is not associated with significant risks or complications. There is minimal pain and little risk for infection or bleeding. Benign cyst fluid is straw colored to dark green to brownish and does not need to be submitted for cytologic evaluation (6). Injection of air into the cyst cavity has been reported to reduce the likelihood of cyst recurrence but is generally

not performed (86). The patient should be reexamined at a short interval thereafter for cyst recurrence. Further cysts will occur in 30% of patients, cause anxiety, and require repeated evaluations (84). **Tissue biopsy should be performed in the presence of the following findings:**

- No cyst fluid is obtained
- The fluid is bloody
- The fluid is thick
- The cyst is complex
- There is an intracystic mass
- A mass persists after aspiration
- A persistent mass is noted at any time during follow-up

Even if a needle biopsy is performed and results are negative for malignancy, a suspicious mass that does not resolve over several months should be excised. Surgery should be conservative, because the primary objective is to exclude cancer. Simple mastectomy or extensive removal of breast tissue is not indicated for fibrocystic disease. Most patients do not require treatment for fibrocystic changes, just reassurance that fibrocystic change is a transient phenomenon of aging that is associated with hormonal effects on the breast glandular tissue that eventually subside.

Fibrocystic Change and Risk for Breast Cancer

Fibrocystic change is not associated with an increased risk of breast cancer unless there is histologic evidence of epithelial proliferative changes, with or without atypia

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(92,93,94,95,96,97). The common coincidence of fibrocystic disease and malignancy in the same breast reflects the fact that both processes are common events. Approximately 80% of biopsies show fibrocystic changes. In an evaluation of the relationship between fibrocystic change and breast cancer in 10,366 women who underwent biopsy from 1950 until 1968 and were followed for a median of 17 years, approximately 70% of the biopsies showed nonproliferative breast disease, whereas 30% showed proliferative breast disease (95). Cytologic atypia were present in 3.6% of cases. Women with nonproliferative disease had no increased risk of breast cancer, whereas women with proliferative breast disease and no atypical hyperplasia had a twofold higher risk of breast cancer. **Patients whose biopsy results showed atypical ductal or lobular hyperplasia had an approximately fivefold higher risk than women with nonproliferative disease to develop invasive breast cancer in either breast.** Patients with carcinoma *in situ* have an eight- to tenfold risk of developing breast cancer. This risk is bilateral for lobular lesions and ipsilateral for ductal lesions. A family history of breast cancer added little risk for women with nonproliferative disease, but

family history plus atypia increased breast cancer risk 11-fold. The presence of cysts alone did not increase the risk of breast cancer, but cysts combined with a family history of breast cancer increased the risk about threefold (76,92,93,94,95,96,97). Women with these risk factors (family history of breast cancer and proliferative breast disease) should be followed carefully with physical examination and mammography. For such women, age-specific probability of developing invasive breast carcinoma in the next 10 years is 1 in 2,000 (age 20), 1 in 256 (age 30), 1 in 67 (age 40), 1 in 39 (age 50), and 1 in 29 (age 60) (93). The relative risk for developing breast cancer depends on the type of proliferative lesion diagnosed.

Management of Fibrocystic Change

Fibrocystic change is a normal evolutionary change in breast development and involution and does not require a specific treatment other than a good clinical breast examination and age-appropriate mammographic screening or imaging studies directed to signs and symptoms. A number of nutritional and dietary supplements have been investigated to relieve symptoms. The role of caffeine consumption in the aggravation of fibrocystic change is controversial (98,99,100,101). Results of some studies suggest that eliminating caffeine from the diet is associated with improvement of symptoms (100,101). Many patients are aware of these studies and report relief of symptoms after discontinuing intake of coffee, tea, and chocolate. Similarly, many women find vitamin E (150–600 IU daily) or B₆ (200–800 mg/day) helpful (102,103). However, observations about these effects have been difficult to confirm and are anecdotal (104,105,106). A recent review of nutritional interventions for fibrocystic breast conditions that evaluated evening primrose oil, vitamin E, or pyridoxine suggested that there are insufficient data to draw clear conclusions about their effectiveness (107). Exacerbations of pain, tenderness, and cyst formation may occur at any time until menopause, when symptoms usually subside unless patients are taking estrogen. **A patient with fibrocystic changes should be advised to examine her own breasts each month just after menstruation and to inform her physician if a mass appears.**

Mastalgia

Mastalgia is a recognized organic condition that has not been studied as thoroughly as other breast problems (108,109). Inflammatory cytokines have been implicated in the etiology of breast pain. A study evaluating expression of interleukin-6 and tumor necrosis factor- α in painful and nonpainful breast tissue showed lower levels of these cytokines in painful breast tissue during the luteal phase; however, these levels did not reach statistical significance (110). Elevated estrogen, low progesterone, or an imbalance in the ratio of estrogen and progesterone have been suggested as a possible cause for the symptoms (111).

Natural History of Mastalgia

Approximately 70% to 80% of women experience severe breast pain at some time in their lives (112,113). Mastalgia accounts for 30% to 47% of breast clinical evaluations (111,114). In 15% of the patients, the mastalgia is so severe that it alters lifestyle and

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requires repeated investigations and treatment (112). Mastalgia interferes with sexual (48%), physical (37%), social (12%), and work or school activities (8%) (115).

Types of Mastalgia

Breast pain is a distressing constellation of symptoms that is classified as cyclic, non-cyclic, or extramammary (116). **Cyclic mastalgia** is related to exaggerated

premenstrual symptoms beginning in the luteal phase of the menstrual cycle associated with breast engorgement, pain, ache, heaviness, and tenderness that is bilateral and can last for more than 7 days in 11% of women (116,117,118). Cyclical mastalgia is more prevalent in women in their third and fourth decades of life and accounts for two thirds of all breast pain symptoms (119). **Noncyclic mastalgia** is independent of menstrual cycles and is described as achy, burning soreness. It may be intermittent or constant, is usually unilateral, occurs in the fourth and fifth decades, and is more difficult to treat than cyclic mastalgia (116). **Extramammary pain** is perceived to be located in the breast but is related to an extramammary site. Chest wall muscular pain, costal cartilage symptoms, herpes zoster, radiculopathies, and rib fractures are among some of the more common causes of extramammary pain. Costochondritis (Tietze's syndrome) is a manifestation of chest wall pain that is frequently interpreted as breast pain.

Management of Mastalgia

Breast pain is an unlikely symptom of malignancy, and once malignancy has been excluded by a clinical breast examination and age-appropriate breast imaging for focal breast pain, the most important treatment is reassurance. Treatments used have included medications, such as anesthetics, diuretics, *bromocriptine*, and *tamoxifen*; vitamins and supplements, such as evening primrose oil; mechanical support with a well-fitting bra; local excision; and decreased fat intake and reduction in methylxanthines from caffeine, tea, and chocolate (108,116). **Discontinuation of hormone therapy may be effective in some women. Maintenance of a pain score diary is important to understand the relationship of pain to factors such as the menstrual cycle, activities of daily living, and stress.** External support may be effective for breast pain associated with generalized fibrocystic changes and is best treated by avoiding trauma and by wearing (night and day) a brassiere that gives good support and protection (120). One study evaluated resolution of symptoms in 200 women randomized either to a regimen of *danazol* (200 mg/day) or to mechanical support with a sports brassiere worn for regular activities for 12 weeks. The group using mechanical support had 85% relief of symptoms compared with 58% improvement in the *danazol* group. Symptoms recurred after discontinuance of treatment with *danazol* (113). The *danazol* group experienced drug-related side effects in 42%, which led to discontinuance of the medication in 15%. The breast has minimal structural support and is at significant risk for motion-related displacement resulting in mastalgia. The use of external support to minimize breast motion appears to be effective in reducing breast pain. The application of heat packs or cold packs and light breast massage may reduce symptoms in some individuals (116).

Hormone-modulating drugs, including *danazol*, *bromocriptine*, *tamoxifen*, and *Depo-provera*, are recognized drug treatments for mastalgia, although *tamoxifen* is not approved for this use in the United States (116,121,122,123,124). These drugs are associated with significant side effects that limit their general use (116). **Withdrawal of birth control pills or hormone therapy may be all that is required to alleviate symptoms** (116).

Danazol is a synthetic androgen that suppresses release of pituitary gonadotropin, prevents luteinizing hormone surge, and inhibits ovarian steroid formation. It is the only medication approved by the Food and Drug Administration for mastalgia (116). The androgenic effects—acne, edema, change in voice, weight gain, headaches, depression, and hirsutism—often are intolerable, and many patients stop taking *danazol* even when symptoms are improved (122). It can be initiated at doses of 100 to 200 mg twice daily orally for patients with severe pain and then tapered to a lower dose of 100 mg per day (122). A survey of surgeons in Great Britain revealed that 75% prescribed *danazol* as first-line

therapy (108). A recent study was conducted to evaluate the response to administration of

danazol (200 mg daily) just during the luteal phase (125). This approach reduced the premenstrual mastalgia and resulted in virtually no side effects.

The use of oral progesterone agents has been shown to reduce cyclical breast pain by 50% (111). Further studies may be warranted to see whether *medroxyprogesterone acetate* suppresses cyclic mastalgia in reproductive-age women.

Breast pain is increased in some individuals who have elevated prolactin (PRL) levels induced by thyrotropin-releasing hormone (TRH) (116). *Bromocriptine* is a dopamine antagonist that inhibits the release of PRL. *Bromocriptine* (2.5 mg twice daily) given for 3 to 6 months is effective in reducing mastalgia in women who have TRH-induced elevation of PRL (123). Patients who have normal TRH levels, or are resistant to *bromocriptine*, or do not tolerate the side effects of nausea, vomiting, and headache, respond favorably to progesterone and systemic nonsteroidal anti-inflammatory drugs (NSAIDs).

Prolactin induces active transport of iodine in breast tissue (126,127). Iodine deficiency in rats causes hyperplasia and atypia (128). Iodine replacement is associated with improvement in subjective pain (129). A randomized, double-blind study with supraphysiologic levels of iodine in women with documented cyclic mastalgia demonstrated dose-dependent reduction in physician-assessed and self-reported pain at 3 and 6 months of treatment (130).

Goserelin is a potent synthetic analog of luteinizing-hormone releasing-hormone (LHRH) that causes reversible reduction in serum estrogen level and decrease in breast pain (131). Side effects of *goserelin* include vaginal dryness, hot flushes, decreased libido, oily skin and hair, and decreased breast size. A recent clinical trial randomized 147 women into *goserelin* versus placebo groups. The study had a 49% dropout rate. The mean breast pain score decreased by 67% in the *goserelin* arm and 35% in the placebo arm. The authors concluded that *goserelin* is an effective treatment for mastalgia with significant side effects and should be kept as second-line therapy. Hormonal blockade of the estrogen receptor is another approach to minimizing the effects of circulating estrogen on breast pain. Treatment with the selective estrogen receptor modulator *tamoxifen* has demonstrated reduction in breast pain at 10 and 20 mg per day, with equivalent effects compared with *danazol* and *bromocriptine* in most studies (124,132,133,134). Topical nonsteroidal therapy is another option for women with mastalgia (135). Gel forms of NSAIDs often are used for relief of pain. Patients were stratified by cyclic versus noncyclic pain and then randomized to treatment with NSAIDs versus placebo. There was a significant reduction in cyclic and noncyclic pain in all groups, but the magnitude of change was greater in the treatment arms and similar for cyclic and noncyclic pain. Use of NSAIDs appears to be a less toxic treatment and may be considered as an option for both cyclic and noncyclic breast pain.

Nonhormonal therapies such as dietary restrictions, vitamins and supplements, and restriction of methylxantines have been investigated as possible treatments for mastalgia because they are less likely to be associated with adverse drug-related side effects (116). Because mastalgia is one of the symptoms associated with fibrocystic disease, the treatments described for fibrocystic disease are also relevant to mastalgia. A low-fat diet was effective in one randomized trial (136). Ninety percent of patients taking in 15% dietary fat experienced resolution of pain symptoms after 6 months compared with only 22% of those on a diet containing 36% fat ($P = 0.0023$). Evening primrose oil containing essential fatty acids (γ -linolenic acid, GLA) has been studied because of its affect on prostaglandin synthesis (137). It has been used as first-line therapy, reserving *danazol* and *bromocriptine* for treatment of more severe symptoms (112). In a small prospective mastalgia trial, women were given eight capsules of evening primrose oil daily for 4 months (320 mg GLA) (138). Those who responded had a lower level of essential fatty acids at the time of initiation when compared with poor responders, suggesting that evening primrose oil increases essential fatty acids and that this increase may be associated with the improvement in

symptoms in the responders. Two more recent trials have failed to demonstrate efficacy of evening primrose oil capsules over placebo (139,140). In a Dutch trial, 124 women with cyclic or noncyclic pain lasting on average 7 or more days (minimum 5 days) were randomized to receive the following regimens: (i) fish oil and control oil, (ii) evening primrose oil and control oil, (iii) fish and evening primrose oil, or (iv) both control oils for 6 months (139). There was a statistically significant reduction in the number of days per month with pain but not in the pain score in the entire study population. There was a greater reduction in cyclic than noncyclic pain symptoms, and this finding was true for both the test oils and for the control oils. The authors concluded that neither fish oil nor evening primrose oil had a better effect than the less expensive wheat germ and corn oils. A second large double-blind randomized prospective trial was conducted in 555 women with cyclic mastalgia of moderate to severe degree present for at least 7 days of a menstrual cycle (140). The four groups were (i) GLA and placebo antioxidants, (ii) placebo fatty acids and antioxidants, (iii) GLA and placebo antioxidants, and (iv) placebo fatty acids and placebo antioxidants. The treatments were given in a blinded fashion for 4 months. All groups had a similar 35% reduction in symptoms. This treatment was followed by open treatment with GLA in all groups and blinded treatment with antioxidants. There was continued improvement of symptoms in all groups with a reduction in mastalgia by 50% over the next 12 months. This is the largest and best-controlled study to date evaluating GLA for relief of mastalgia, and GLA was not found to be superior to placebo. The results of this study were not consistent with those from previous smaller studies. The authors cannot exclude a significant psychologic impact that may confound the effect of GLA. GLA use was found to be safe, without any significant side effects, and has been prescribed as therapy for mastalgia because of its lack of side effects. The recent randomized trials, however, bring into serious question the efficacy of these options.

Fibroepithelial Lesions

Fibroadenoma

Fibroadenomas are the most common benign tumors of the breast. In one series, they accounted for 50% of all breast biopsies (141). They usually occur in young women (age 20–35 years) and may occur in teenagers (142). In women younger than 25 years, fibroadenomas are more common than cysts. They rarely occur after menopause, although occasionally they are found, often calcified, in postmenopausal women. For this reason, it is postulated that fibroadenomas are responsive to estrogen stimulation. A recent study reports the *de novo* occurrence of fibroadenoma in 51 women older than age 35 years who had no evidence of a palpable or mammographic visualized lesion in well-documented prior visits (143). Fibroadenomas may appear as single masses or as multiple lesions.

Clinically, a young woman usually notices a mass while showering or dressing. Most masses are 2 to 3 cm in diameter when detected, but they can become extremely large (i.e., the giant fibroadenoma). On physical examination, they are firm, smooth, and rubbery. They do not elicit an inflammatory reaction, are freely mobile, and cause no dimpling of the skin or nipple retraction. They are often bilobed, and a groove can be palpated on examination. On mammographic and ultrasonographic imaging, the typical features are of a well-defined, smooth, solid mass with clearly defined margins and dimensions that are longer than wide and craniocaudad dimensions that are less than the length.

Fibroadenoma is not associated with an increased risk for breast cancer (144). The natural history of fibroadenoma can be regression, growth, or no change in size. In one study, a 50% regression was reported (145). Because transformation of a fibroadenoma into cancer is

rare and regression is frequent, current management recommendations are conservative unless there is evidence of growth (141). A suspected fibroadenoma should be confirmed by FNAC or CNB and observed for increase in size or excised based on patient preference. Rarely will the fibroadenoma increase to more than 2 to 3 cm in size. Large or

growing fibroadenomas must be excised. Complete excision of a fibroadenoma with local anesthesia can be performed to treat the lesion and confirm the absence of malignancy. Less invasive local treatment of a fibroadenoma is advocated by some and can be performed with either ultrasonographically guided percutaneous vacuum-assisted biopsy devices (146) or percutaneous cryoablation (147). However, a young woman with a clinical fibroadenoma can undergo needle cytology and observation of the mass (148). Acceptance of observation varies, and many women choose to have the fibroadenoma excised (149).

On gross examination of an excised mass, the fibroadenoma appears encapsulated and sharply delineated from the surrounding breast parenchyma. Microscopically, there is proliferation of both the epithelial and a stromal component. In long-standing lesions and in postmenopausal patients, calcifications may be observed within the stroma.

Multiple Fibroadenomas

Multiple fibroadenomas occur in some women and have been reported to occur more frequently in premenopausal women undergoing immunosuppression for transplant (150,151,152). Excision of all lesions through separate incisions could leave significant scarring and deformity. Excision of these mobile lesions through a single periareolar incision has been suggested, but this approach can lead to significant ductal disruption (153). Another approach that has been used is through an incision in the inframammary crease. Alternatively, these lesions can be treated with observation based on triple-test concordance of results of a classic clinical examination with histologic corroboration with FNAC and ultrasonographic diagnostic criteria consistent with a fibroadenoma (151).

Phyllodes Tumor

Phyllodes tumors are rare fibroepithelial tumors that display a spectrum of clinical and pathologic behaviors that are benign, borderline, and malignant (154,155).

The distribution of phyllodes tumors demonstrates that **most tumors are benign (70%) compared with malignant (23%) and borderline lesions (7%)** (156). This distribution is similar to a larger, older study that reported an incidence of 64% benign, 21% malignant, and 14% borderline phyllodes tumors (157). The incidence in some studies should be viewed with caution because of variation in histologic interpretation (156).

Phyllodes tumors may occur at any age but tend to be more common in women who are in their late 30s, 40s, and 50s (156,158,159,160,161,162). **These lesions are rarely bilateral and usually appear as isolated masses that are difficult to distinguish clinically from a fibroadenoma.** Patients often relate a long history of a previously stable nodule that suddenly increases in size. Reported sizes range from 1.0 to 50 cm (154,163,164). Size is not a dependable diagnostic criterion, although phyllodes tumors tend to be larger than fibroadenomas, probably because of their rapid growth. There are no good clinical criteria by which to distinguish a phyllodes tumor from a fibroadenoma. Whereas observation of a fibroadenoma is acceptable, excision of a phyllodes tumor is necessary for local control and for determination of benign or malignant features. To avoid unnecessary excision of benign fibroadenomas that are indistinguishable from phyllodes tumors on clinical examination, imaging criteria have been sought to aid in identifying patients who require EB for complete histopathologic evaluation and local control. Mammography may show a halo around

a phyllodes tumor mass but cannot reliably distinguish a fibroadenoma from a phyllodes tumor (165,166,167). Ultrasonography evaluation also has limitations even when color and pulse Doppler ultrasonography are used in conjunction with it (163).

Microscopic evaluation of a lesion is important to determine the diagnosis. The histologic distinction between fibroadenoma, benign, borderline, and malignant phyllodes tumor can, however, be very difficult on minimal tissue sampling with FNAC or CNB (168,169). It may be easier to distinguish benign phyllodes from malignant phyllodes tumors than benign phyllodes tumors from fibroadenomas (170). Histologic features that stratify lesions include number of mitoses per high power field, stromal cellularity, pushing or infiltrating tumor margin, cellular atypia, tumor necrosis, and stromal overgrowth (171).

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If a lesion cannot clearly be characterized as a fibroadenoma, excision may be necessary. Factors that are considered in recommending excision include older age, new mass in a well-screened individual, rapid growth, size greater than 2.5 to 3 cm, suspicious FNAC or CB, and mammographic or ultrasonographic features that demonstrate lobulation and intramural cysts. If observation is elected, repeat clinical examination and imaging in a short interval is essential to evaluate change in size.

Treatment of biopsy-proven phyllodes tumor is wide local excision, attempting to obtain a 1- to 2-cm margin (156,157,158,159,160,161). Massive tumors, or large tumors in relatively small breasts, may require mastectomy; otherwise, mastectomy should be avoided, and axillary lymph node dissection is not indicated. Often, however, a patient will undergo excisional biopsy of a mass believed to be fibroadenoma, and final histologic examination reveals a phyllodes tumor. Re-excision with normal breast margins is recommended for borderline and malignant phyllodes tumors (159). An expectant approach is an option for unanticipated diagnosis of benign phyllodes tumors (157).

The prognosis of benign and malignant phyllodes tumors is variable (154,155,157,162,172). **Tumors judged to be benign phyllodes tumors can recur locally in up to 10% of patients** (159,160,161). Recurrence is associated with margin involvement, whereas mortality correlates with size and grade (173). In a series reviewing only high-grade malignant phyllodes tumors, size and excision margins were associated with local recurrence and metastatic spread, and mastectomy may be required to achieve complete surgical excision (174). **Malignant phyllodes tumors tend to recur locally and occasionally may metastasize to the lung, although brain, pelvic, and bone metastases also may occur** (160,161,162). The stromal component of the tumor is malignant and metastasizes, behaving like a sarcoma. Axillary involvement is extremely unusual. Often, the appearance of metastasis is the first sign that a phyllodes tumor is malignant. Chemotherapy for metastatic phyllodes tumors should be based on regimens for sarcoma, not adenocarcinoma (159). Radiation therapy has generally not been used in the treatment of phyllodes tumors. In the presence of a bulky tumor, positive margins, recurrence, or malignant histology, radiation therapy may be of some benefit (175).

Breast Conditions Requiring Evaluation

Nipple Discharge

Nipple discharge is a presenting breast symptom in 4.5% of patients seeking evaluation of a breast symptom, with 48% spontaneous and 52% provoked (176). Nipple discharge that does not occur spontaneously has no pathologic significance. Provoked or self-induced nipple discharge should be managed by reassurance and instruction to discontinue

manipulation. Spontaneous nipple discharge is more likely to be associated with an underlying pathologic problem than provoked discharge. **Although it is a distressing finding, spontaneous nipple discharge is infrequently found to be associated with carcinoma, ranging from 4% to 10% (176,177,178).** Nipple discharge can be caused by neoplastic or nonneoplastic processes (179). Nonneoplastic processes include galactorrhea, physiologic changes resulting from mechanical manipulation, parous condition, periductal mastitis, subareolar abscess, fibrocystic change, and mammary duct ectasia. Neoplastic causes of nipple discharge in nonlactating women are solitary intraductal papilloma, carcinoma, papillomatosis, squamous metaplasia, and adenosis (176,179,180). Extramammary causes are related to hormones and drugs (179). **Following are the important characteristics of the discharge and other factors to be evaluated by history and physical examination (180):**

- Nature of discharge (serous, bloody, or milky)
- Association with a mass

- Unilateral or bilateral
- Single or multiple ducts
- Discharge that is spontaneous (persistent or intermittent) or expressed by pressure at a single site or on entire breast
- Relation to menses
- Premenopausal or postmenopausal
- Hormonal medication (contraceptive pills or estrogen)

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Unilateral, spontaneous, bloody, or serosanguinous discharge from a single duct is usually caused by an intraductal papilloma or, rarely, by an intraductal cancer. In either case, a mass may not be palpable. The involved duct may be identified by pressure at different sites around the nipple and at the margin of the areola. Bloody discharge is more suggestive of cancer but usually is caused by a benign papilloma in the duct. In premenopausal women, spontaneous multiple-duct discharge, unilateral or bilateral, is most marked just before menstruation. It often is caused by fibrocystic change. Discharge may be green or brownish. Papillomatosis and ductal ectasia are usually seen on biopsy. If a mass is present, it should be removed. Milky discharge from multiple ducts in nonlactating women presumably reflects increased secretion of pituitary prolactin; serum prolactin and thyroid-stimulating hormone levels should be evaluated to detect a pituitary tumor or hypothyroidism. Hypothyroidism may cause galactorrhea. Alternatively, *phenothiazines* may cause milky discharge that disappears when the medication is discontinued. Oral contraceptive agents may cause clear, serous, or milky discharge from multiple ducts or, less often, from a single duct. The discharge is more evident just before menstruation and

disappears when the medication is stopped.

Chronic unilateral nipple discharge, especially if it is bloody, is an indication for resection of the involved ducts. Mammography and ultrasonography are performed to rule out an associated mass. On occasion, ductography may be performed to identify a filling defect before excision of the duct system, but usually this technique is of little value (178). Ductography, however, is not a substitute for excision because it misses multiple lesions and cannot visualize the periphery (181).

A new technology, fiberoptic ductoscopy, is emerging to evaluate patients with nipple discharge (182). In 259 patients with nipple discharge, fiberoptic ductoscopy successfully detected intraductal papillary lesions in 92 patients (36%). Office-based minimally invasive breast ductoscopy with intraductal biopsy is available in some centers (183,184). It was performed for diagnosis in 83 patients with nipple discharge (183). A diagnosis of severe or malignant atypia was established in 21% of patients.

Cytologic examination of nipple discharge or cyst fluid rarely is performed. **Cytologic examination usually is of no value but may identify malignant cells** (178). Negative findings do not rule out cancer, which is more likely in women older than 50 years of age. In any case, the involved duct—and a mass, if present—should be excised (177,178,180,185). Complete histopathologic evaluation of the involved ductal system is the preferred method of diagnosis, and cytologic assessment should not be relied on for diagnosis.

The usual approach for nipple discharge is surgical excision through a periareolar incision adjacent to the trigger point, the pressure point that elicits nipple discharge (179). A microdochetomy of a single duct or a central duct excision of the major subareolar ducts can be performed under local or general anesthesia. The putative duct can be cannulated,

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methylene blue can be injected, or a lacrimal probe can be inserted into the duct for localization. A resection of breast tissue for 3 to 5 cm, or until no bloody fluid can be identified in the ductal system, is performed. The patient must be warned of possible skin and nipple loss as a result of compromised vascularity, change in nipple sensation, deformity, inability to breastfeed, and recurrence if only a single duct is removed.

When there is a history of unilateral nipple discharge, localization is not possible, and no mass is palpable, the patient should be reexamined every week for 1 month. When unilateral discharge persists, even without definite localization or tumor, surgical exploration should be considered. The alternative is careful follow-up at intervals of 1 to 3 months.

Mammography should be performed. Purulent discharge may originate in a subareolar abscess and requires excision of the related lactiferous sinus (186).

Erosive Adenomatosis of the Nipple

Erosive adenomatosis is a rare benign condition of the nipple that mimics Paget's disease (187). Patients seek treatment for pruritus, burning, and pain. On clinical examination, the nipple can appear ulcerated, crusting, scaling, indurated, and erythematous. The nipple can be enlarged and more prominent during menstrual cycles (188). The differential diagnosis includes squamous cell carcinoma, psoriasis, contact dermatitis, seborrheic keratosis, adenocarcinoma metastatic to the skin, and unusual primary tumors of the nipple (187). Biopsy should be performed to diagnose the lesion. Local excision is curative (187).

Fat Necrosis

Fat necrosis of the breast is rare but clinically important because it produces a mass,

often accompanied by skin or nipple retraction, which is indistinguishable from carcinoma. Fat necrosis often presents as a confusing clinical finding. Trauma is presumed to be the cause, although only about one half of patients have a history of injury to the breast. Ecchymosis is occasionally seen near the tumor. Tenderness may or may not be present. If untreated, the mass associated with fat necrosis gradually disappears. Diagnostic imaging studies are usually insufficient (189). As a rule, the safest course is needle-core or excisional biopsy of the entire mass to rule out carcinoma (189). Fat necrosis is also common after segmental resection and radiation therapy or transverse rectus abdominis musculocutaneous (TRAM) flap (190).

Breast Abscess

Lactational Abscesses

Infection in the breast is rare unless the patient is lactating. Lactational mastitis must be distinguished from lactational abscess (191). During lactation, an area of redness, tenderness, and induration frequently develops in the breast. **Lactational mastitis is caused by transmission of bacteria during nursing and poor hygiene. The organism most commonly found in lactational mastitis and abscesses is *Staphylococcus aureus*** (192). If mastitis is diagnosed, manual pressure, antibiotics, and continued breastfeeding are recommended. In its early stages, the infection often can be treated while breastfeeding is continued by administering an antibiotic such as *dicloxacillin* 250 mg four times daily, or *oxacillin*, 500 mg four times daily for 7 to 10 days. **If the lesion progresses to a localized mass with local and systemic signs of infection, an abscess is present. It should be drained, and breastfeeding should be discontinued.**

Nonlactational Abscess

Rarely, infections or abscesses may develop in young or middle-aged women who are not lactating (193). The current approach to nonlactational abscess is conservative (194,195). A suspected abscess should be evaluated with preliminary ultrasonography to detect the

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presence of an inflammatory mass, frank pus, solitary cavity, or a multiloculated abscess (196). Aspiration of pus, if present, and antibiotic therapy is instituted with reaspiration, if necessary (196). When the fluid collection is greater than 3 mL, percutaneous drain placement is an option (194). A single aspiration is sufficient in about one half of patients (194). Recurrent abscess formation is low (10%) (194). Bacteriologic analysis of 22 abscesses in nonlactating women shows a preponderance of gram-positive cocci, including *Staphylococcus epidermidis* (11 women), *Staphylococcus aureus* (3 women), *Proteus mirabilis* (3 women), *Pseudomonas aeruginosa* (1 woman), and sterile abscess (4 women) (196). **If these infections recur after multiple aspirations, incision and drainage followed by excision of the involved lactiferous duct or ducts at the base of the nipple may be necessary during a quiescent interval.** In virtually all cases, mammillary sinus (lactiferous duct fistula) can be confirmed as the cause of reinfection or persistent infection (197). Inflammatory carcinoma is a consideration when erythema of the breast is present. Patients should not undergo prolonged treatment for an apparent infection unless biopsy has eliminated the possibility of inflammatory carcinoma.

Subareolar Abscess and Lactiferous Duct Fistula

Subareolar abscess and fistula of the lactiferous ducts secondary to squamous metaplasia can

occur (198). The distal duct can be occluded with inspissated debris. Two large recent reviews report a high association of lactiferous duct fistulae in women who smoke (199,200). The definitive treatment for lactiferous duct sinus is excision of the lactiferous duct and drainage of the abscess cavity. In both studies, **the recurrence rate was greater when only incision and drainage were performed**. The most common organism occurring in primary subareolar abscess was *Staphylococcus aureus*, but anaerobic organisms occurred more frequently in chronic recurring abscesses (200).

Disorders of Breast Augmentation

Estimates indicate that nearly 4 million women in the United States have undergone augmentation mammoplasty. Breast implants are usually placed under the pectoralis muscle or, less desirably, in the subcutaneous tissue of the breast. Most implants are made of an outer silicone shell filled with a silicone gel or saline.

The complications of breast implantation are significant. About 15% to 25% of patients develop capsule contraction or scarring around the implant, leading to a firmness and distortion of the breast that can be painful and sometimes requires removal of the implant and capsule. Implant rupture may occur in as many as 5% to 10% of women, and bleeding of gel through the capsule is even more common (201).

In April 1992, the U.S. Food and Drug Administration concluded that the safety and effectiveness of silicone gel breast implants had not been established and called for additional preclinical and clinical studies (202). The agency advised symptomatic women with ruptured implants to discuss the need for surgical removal with their physicians. When there is no evidence of associated symptoms or rupture, implant removal is generally not indicated because the risks of removal are probably greater than the risk of retention. If screening ultrasonography shows no rupture, the probability of rupture is 2.2% (203). If ultrasonography shows rupture, true rupture is present in 37.8%. In this setting, a large number of women would have normal implants removed. When MRI is used in addition to ultrasonography, the probability of rupture increases to 86%.

The suggested association between silicone gel and autoimmune disease has been poorly documented (204,205). A retrospective cohort study from the Mayo Clinic showed no increased incidence of autoimmune disorders among women with silicone implants (206). Subsequent studies have demonstrated no clinical data proving an increased incidence of connective tissue disorders in patients with silicone gel breast implants (207,208,209). The data continue to reaffirm previous observations that there is no evidence of an association between breast implants and connective tissue diseases (210). In a study of Danish

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women undergoing reduction mammoplasty compared with silicone implant augmentation, there was no increased incidence of antinuclear antibodies or other autoantibodies between the groups (211). The augmentation group experienced capsular contraction and more pain than the group undergoing reduction mammoplasty. Any association between implants and an increased incidence of breast cancer is unlikely (212). However, breast cancer may develop in any patient with a silicone gel prosthesis.

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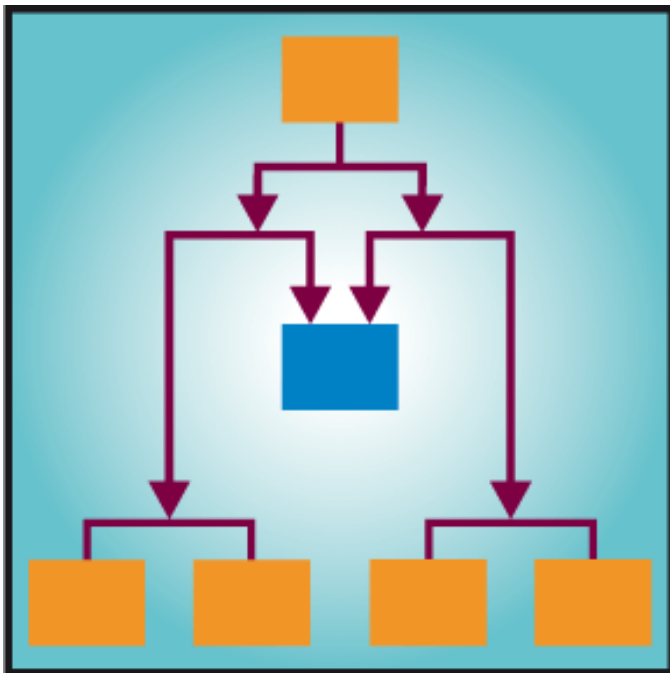
Preoperative Evaluation and Postoperative Management

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- **The preoperative evaluation should be complete and thorough, taking into account the essential aspects of the patient's general medical condition and prior surgical history. The risks and potential complications of the surgical procedure should be discussed with the patient, including the most frequent complications of the particular surgical procedure.**
- **The calculated body mass index (BMI) can be used as a surrogate marker for nutritional status.**
- **Careful and meticulous fluid and electrolyte management is essential for all patients undergoing major surgical procedures.**
- **Although satisfactory analgesia is easily achievable with currently available methods, patients continue to suffer unnecessarily from**

postoperative pain.

- **Prophylactic antibiotics should be employed judiciously. Prompt identification of perioperative infections and their specific treatments are critical to minimize the impact of this common morbidity.**
 - **Early in its clinical course, a postoperative small bowel obstruction may exhibit signs and symptoms identical to those of ileus. Initial conservative management as outlined for the treatment of ileus is appropriate.**
 - **Because pulmonary embolism is the leading cause of deaths following gynecologic surgical procedures, identification of high-risk patients and the use of prophylactic venous thromboembolism regimens is an essential part of management. Calf compression during and after gynecologic surgery significantly reduces the incidence of deep venous thrombosis on a level similar to that of low-dose *heparin*.**
-
- **Patients who are predisposed to cardiovascular, respiratory, and endocrine illnesses must be thoroughly screened preoperatively. Coronary artery disease is a major risk factor for patients undergoing abdominal surgery. Patients with hypertension should receive medication to control their disease before surgery. Chronic obstructive pulmonary disease is the greatest risk factor for the development of postoperative pulmonary complications. Perioperative management of medical complications must be prompt and meticulous.**

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The successful outcome of gynecologic surgery is based on thorough evaluation, careful preoperative preparation, and attentive postoperative care. Discussed in this chapter are

approaches to the general perioperative management of patients undergoing major gynecologic surgery with specific medical problems that could complicate the surgical outcome.

Medical History and Physical Examination

Gynecologic surgery should only be undertaken after gaining a thorough understanding of a patient's medical history and performing a complete physical examination.

- **The medical history should include detailed questions to identify any medical illnesses that might be aggravated by surgery or anesthesia.** Coronary artery disease and pulmonary diseases are the most common sources of postoperative complications.
- **Medications currently being taken (including nonprescription drugs) as well as those discontinued within the previous month before surgery should be recorded.** In addition, information about the use of "alternative therapies," herbs, and vitamins should be elicited. Specific instructions must be given to the patient regarding the need to discontinue any medications before surgery (e.g., aspirin, antiplatelet agents, or oral contraceptives), as well as those medications that should be continued (e.g., cardiac or antihypertensive medications).
- **The patient should be questioned regarding known allergies to medications (e.g., sulfa and penicillin), foods, or environmental agents.** A history of sensitivity to shellfish may be the only clue of iodine sensitivity, which could be fatal if intravenous contrast materials are used without corticosteroid preparation.
- **Previous surgical procedures, and the patient's course following those surgical procedures, should be reviewed to identify potential complications that might be avoided.** The patient should be asked about specific complications, such as excessive bleeding, wound infection, deep venous thrombosis, peritonitis, or bowel obstruction. A history of pelvic surgery should alert the gynecologist to the possibility of distorted surgical anatomy and pre-existing injury to adjacent organ systems such as small bowel adhesions or ureteral stenosis from previous periureteral scarring. In such cases, it may be prudent to identify any

pre-existing abnormality by performing intravenous pyelography (IVP) or computed tomography (CT). Many patients may not be entirely clear about the extent of the previous surgical procedure or the details of intraoperative findings. Therefore, operative notes from previous procedures should be obtained and reviewed.

- **Family history may identify familial traits that might complicate planned surgery.** A family history of excessive intraoperative or postoperative bleeding,

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venous thromboembolism, malignant hyperthermia, and other potentially inherited conditions should be sought.

- **A review of systems should also be detailed to identify any coexisting medical or surgical conditions.** Inquiry about gastrointestinal and urologic function is particularly important before undertaking pelvic surgery because many gynecologic diseases also involve adjacent nongynecologic viscera.
- **Although many women undergoing gynecologic surgical procedures are otherwise healthy, with pathology identified only on pelvic examination, other major organ systems should not be neglected in the physical examination.** Identification of abnormalities, such as a heart murmur or pulmonary compromise, should lead the surgeon to obtain additional testing and consultation to minimize intraoperative and postoperative complications.

Laboratory Evaluation

The selection of appropriate preoperative laboratory studies depends on the extent of the anticipated surgical procedure and the patient's medical status.

- For patients undergoing general anesthesia, a blood count including hematocrit, white cell

count, and platelet count should be obtained routinely.

- Serum chemistry and liver function test results rarely are abnormal in asymptomatic patients who have no significant medical history and who are not taking medications.
- Coagulation studies are of little value unless the patient has a significant medical history (1).
- In women younger than 50 years of age, a chest x-ray and electrocardiography are of very low yield in identifying asymptomatic cardiopulmonary disease and thus are not necessary (2,3).

Detailed evaluation of adjacent organ systems should be undertaken in individual cases as follows:

- CT urography is helpful to delineate ureteral patency and course, especially in the presence of a pelvic mass, gynecologic cancer, or congenital müllerian anomaly. However, a CT urogram is not of value in the evaluation of most patients undergoing pelvic surgery (4).
- Upper endoscopy, colonoscopy, barium enema, or upper gastrointestinal studies with small bowel assessment may be of value in evaluating some patients before undergoing pelvic surgery. Because of the proximity of the female genital tract to the lower gastrointestinal tract, the rectum and sigmoid colon may be involved with benign (endometriosis or pelvic inflammatory disease) or malignant gynecologic conditions. Conversely, a pelvic mass could have a gastrointestinal origin such as a diverticular abscess or a mass of inflamed small intestines (Crohn's disease) or, rarely, a gastric or pancreatic carcinoma. Clearly, any patient with gastrointestinal symptoms should be further evaluated.
- Other imaging studies, including ultrasonography, CT scanning, or MRI, may be useful in selected patients.

Preoperative Discussion and Informed Consent

The preoperative discussion should include a description of the surgical procedure, its expected outcome, and risks; it is the basis for obtaining signed informed consent

(5). Informed consent is an educational process for the patient and her family and fulfills the physician's need to convey information in understandable terms. The items listed in Table 20.1 should be discussed, and, after each item, the patient and family should be invited to ask questions.

Table 20.1 Outline of Key Points of the Preoperative Informed Consent Discussion

- | |
|---|
| 1. The nature and extent of the disease process |
| 2. The extent of the actual operation proposed and the potential modifications of the operation, depending on intraoperative findings |
| 3. The anticipated benefits of the operation, with a conservative estimate of successful outcome |
| 4. The risks and potential complications of the surgery |
| 5. Alternative methods of therapy and the risks and results of those alternative methods of therapy |
| 6. The results likely if the patient is not treated |

Following are components of the informed consent process:

- **A discussion of the nature and the extent of the disease process should include an explanation in lay terms of the significance of the disease or condition.** Printed materials, computer-based learning programs, and videotapes may assist in this process.
- **The goals of surgery should be discussed in detail.** Some gynecologic surgical procedures

are performed purely for diagnostic purposes (e.g., dilation and curettage, cold knife conization, diagnostic laparoscopy), whereas most are aimed at correcting a specific problem. The extent of the surgery should be outlined, including which organs will be removed. Most patients like to be informed regarding the type of surgical incision and the estimated duration of anesthesia.

- **The expected outcome of the surgical procedure should be explained.** If the procedure is being performed for diagnostic purposes, the outcome will depend on surgical or pathologic findings that are not known before surgery. When treating an anatomic deformity or disease, the expected success of the operation should be discussed, as well as the potential for failure of the operation (e.g., failure of tubal sterilization or the possibility that stress urinary incontinence may not be alleviated). When treating cancer, the possibility of finding more advanced disease and the potential need for adjunctive therapy (e.g., postoperative radiation therapy or chemotherapy) should be mentioned. Other issues of importance to the patient include discussion of loss of fertility or loss of ovarian function. These issues should be raised by the physician to ensure that the patient adequately understands the pathophysiology that may result from the surgery and to allow her to express her feelings regarding these emotionally charged issues. Unanticipated findings at the time of surgery should also be mentioned. For example, if the ovaries are unexpectedly found to be diseased, the best surgical judgment may be that they should be removed.

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- **The risks and potential complications of the surgical procedure should be discussed with the patient, including the most frequent complications of the particular surgical procedure.** For most major gynecologic surgery, the risks include intraoperative and postoperative hemorrhage, postoperative infection, venous thromboembolism, injury to adjacent viscera, and wound complications. If the patient has a preexisting medical problem (e.g., diabetes, obesity, chronic obstructive pulmonary disease [COPD], coronary artery disease) additional risks should be reviewed.

- **The usual postoperative course should be discussed in enough detail to allow the patient to understand what to expect in the days following surgery.** Information

regarding the need for a suprapubic catheter or prolonged central venous monitoring helps the patient accept her postoperative course and avoids surprises to the patient that may be disconcerting. The expected duration of the recovery period, both in and out of the hospital, should be outlined.

- **Alternative methods of therapy should be discussed, including medical management or other surgical approaches.** The patient should also have an understanding of the outcome of the disease if nothing is done.

General Considerations

Nutrition

In general, young patients undergoing elective gynecologic surgery have adequate nutritional stores and, for the most part, do not require nutritional support. However, **all patients should have a nutritional assessment, especially elderly patients and those undergoing gynecologic cancer surgery or other major gynecologic procedures in which a prolonged postoperative recovery is expected.** Nutritional status should be reassessed at regular intervals postoperatively until the patient has successfully returned to a regular diet.

A nutritional assessment includes a careful history and physical examination, which are the most useful, reliable, and cost-effective methods of determining a patient's nutritional status. In particular, information about recent weight loss, dietary history, fad diets, extreme exercise, or anorexia or bulimia should be elucidated. Physical evidence of malnutrition includes temporal wasting, muscle wasting, ascites, and edema. Accurate height and weight measurements should be obtained and an ideal body weight, percent ideal body weight, and percent usual body weight may be calculated. Many Internet-based body weight calculators are available. A variety of techniques have been developed to determine a patient's nutritional state; however, many methods lack clinical utility outside of a research setting.

Anthropometric measurements of skinfold thickness and arm-muscle circumference provide an estimate of total body fat and lean muscle mass.

The calculated body mass index (BMI) can be used as a surrogate marker for nutritional status.

The BMI is calculated as body weight in kilograms divided by the height in square centimeters. A BMI less than 22 increases the risk of malnutrition, and a BMI less than 19 gives clear evidence of malnutrition (6).

Patients who have lost less than 6% of their ideal body weight do not need preoperative nutritional intervention. However, **patients who have lost more than 10% of their ideal body weight in 6 months meet the definition of severely malnourished and should be considered for preoperative intervention (7).** Patients who have lost between 6% and 12% should undergo further studies to determine if preoperative intervention is needed. Laboratory assessments of albumin, transferrin, zinc, lipids, and liver function may be obtained in addition to the routine preoperative tests. The degree of malnutrition can in

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part be determined by serum concentrations of albumin, transferrin, and prealbumin. The levels of these serum proteins are greatly influenced by the patient's level of hydration. Prealbumin has the shortest half-life, at 2 to 3 days, and levels of this protein are depressed very early in comparison with serum transferrin and albumin, which have half-lives of 8 and 20 days, respectively (8). Serum albumin was determined to be a substitute for the Prognostic Nutritional Index, which is a time-consuming calculation, in assessing malnutrition in women with gynecologic malignancies (9). **A serum albumin level of 3.5 to 5.0 is in the normal range, 2.8 to 3.4 is considered to indicate mild malnutrition, 2.1 to 2.7 moderate malnutrition, and less than 2.1 severe malnutrition (10).**

Hypoalbuminemia is correlated with morbidity, mortality, and increased postoperative complication rates in data from the National Surgical Quality Improvement Program (11). Decisions regarding the need for nutritional support should be based on several individualized factors. These factors include the patient's prior nutritional state, the anticipated length of time in which the patient will not be able to eat, the severity of surgery, and the likelihood of complications. The nutritional assessment should also determine whether the cause of the malnutrition is increased enteral loss (malabsorption, intestinal fistula), decreased oral intake, increased nutritional requirements as a result of hypermetabolism (sepsis, malignancy), or a combination of these factors. Severe malnutrition, if not corrected, can further complicate the postoperative problem by causing altered immune function, chronic anemia, impaired wound healing, and eventually multiple organ system failure and death.

The patient's nutritional requirements are increased by surgery for several reasons. First, there is a period following surgery during which oral intake is not allowed or is very limited. In addition, the operation itself causes increased protein catabolism, increased energy requirements, and a negative nitrogen balance. If the surgery is uncomplicated and the patient is without food for less than 7 days, this response is limited and patients usually recover without the need for nutritional support. An adequate diet is defined as providing 75% of estimated caloric and protein needs. Therefore, **if an adequate oral diet is not expected for 7 to 10 days, perioperative nutritional support may be required to avoid progressive malnutrition and associated complications** (10). Perioperative nutritional support reduces operative morbidity and decreases the length of hospitalization when commenced early in the postoperative course. Therefore, patients with either normal nutritional indices or mild or moderate malnutrition, who will be undergoing surgical procedures likely to require a prolonged catabolic period of more than 7 to 10 days, should have enteral or parenteral nutrition instituted in the early postoperative period as soon as the patient is hemodynamically stable. This type of management should be strongly considered in patients undergoing pelvic exenterations, urinary diversions, or multiple enterectomies (12). Preoperative nutritional support is indicated for patients who have significant preexisting malnutrition or require major elective surgery. **According to the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, evidence-based medicine supports the use of preoperative nutritional support for 7 to 14 days in moderately to severely malnourished patients undergoing major nonemergent, gastrointestinal surgery** (8). A Veterans Affairs Total Parenteral Nutrition Cooperative Study found that severely malnourished patients preconditioned with total parenteral nutrition (TPN) had fewer complications than did control patients, excluding infectious complications (13). In a meta-analysis review of 22 studies of preoperative TPN use, a 10% decrease in postoperative complications occurred in TPN-supported patients (14). Although encouraging, these findings are controversial and not supported by all studies or meta-analyses (15). If preoperative TPN is prescribed, it should be tapered and stopped at midnight before surgery, restarted 24 to 72 hours after the procedure, and continued until the patient is able to meet nutritional requirements.

ASPEN guidelines do not support the routine use of nutritional support in the immediate postoperative period for patients undergoing major gastrointestinal surgery; however, the guidelines do indicate a role for nutritional support postoperatively in patients in whom

oral intake will be inadequate for 7 to 10 days (8). In summary, clinical trials have demonstrated that TPN can improve nutritional status as measured by biochemical assays, immune function, and nitrogen balance. The effect of TPN on clinical outcome, however, is less well established. **Despite what would seem reasonable based on common sense as well as preoperative nutritional parameters, the data do not support TPN for mild to moderately malnourished patients. With severe malnutrition, preoperative TPN would seem to be beneficial and should be instituted.**

Route of Administration

After the decision has been made that nutritional support is required, the appropriate route of administration must be determined. **Enteral nutrition should be considered primarily because it is easy to deliver, associated with the fewest complications, linked to enhanced wound healing, and relatively inexpensive** (16). Contraindications to this route of delivery include intestinal obstruction, gastrointestinal bleeding, and diarrhea. Many different types of preparations are commercially available and can be chosen based on their caloric content, fat content, protein content, osmolality, viscosity, and price. Depending on the patient's problem, the route of delivery may be through a Dobhoff feeding tube, a gastrostomy tube, or a feeding jejunostomy tube (17). If the gastrointestinal tract is unusable for more than 7 days postoperatively, TPN should be implemented.

Total parenteral nutrition must be delivered through a central vein and has gained wide acceptance as a means of providing nutritional support for surgically ill patients. It must be delivered through a subclavian or internal jugular vein, and the catheter must be placed using meticulous sterile surgical technique. Only intravenous access lines in the right atrium, superior vena cava, or inferior vena cava can be truly deemed central lines (18). Proper daily care is required to avoid infectious complications. When managed by an experienced team, the most frequent complication, infection, can be reduced to a very reasonable level (19).

Composition of Total Parenteral Nutrition Solutions

Calories. The daily caloric requirements can be met by providing **1,000 calories more than the patient's basal energy expenditure.** Caloric requirements can be calculated based on **Long's modification of the Harrison-Benedict formula** for actual energy expenditure (AEE) (20). This is the most accurate available method to calculate an individual's AEE:

$$\text{AEE (women)} = [655.10 + 9.56 \text{ Weight (kg)} + 1.85 \text{ Height (cm)} - 4.68 \text{ Age (yrs)}] \times (\text{activity factor}) \times (\text{injury factor})$$

Activity factor: confined to bed (1.2), out of bed (1.3).

Injury factor: minor surgery (1.2), skeletal trauma (1.3), major sepsis (1.6), severe burn (2.1).

Alternatively, daily caloric requirements can be met by giving the patient 35 kcal/kg/day for maintenance and 45 kcal/kg/day for anabolic states.

- **Protein.** Daily nitrogen requirements may be met by providing **1 g of nitrogen (6.25 g of protein) for every 130 to 150 calories.** Protein is provided by synthetic amino acids. **The amino acids provide 15% to 20% of total calories** (19).

- **Carbohydrates.** The carbohydrate base of TPN is dextrose (glucose) in approximately 25% solution. Adults need approximately 100 g of dextrose per day at baseline. However, the maximal rate of glucose oxygenation in adults is approximately 7 g/kg/day, and glucose administration in excess of the caloric requirements can lead to fatty infiltration of the liver and other metabolic complications.

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When given by TPN infusion, the dextrose tolerance in critically ill patients is 5 mg/kg/minute (19). Insulin should be used to maintain serum glucose concentration between 150 and 250 mg/dL, and it may be added directly to the TPN solution.

- **Fats.** Lipids in a 10% to 20% emulsion can be given as further caloric supplement and supply the essential fatty acids, linoleic acid, and alpha-linoleic acids. More calories can be given in the form of free fatty acids, which are the major source of energy for most peripheral tissues. When lipids are used as a major source of calories, a minimum of 50 to 150 g/day of glucose should also be given to provide a substrate for the central nervous system. Most patients

can tolerate up to 2 g of fat/kg/day, and daily dosages should not exceed 4 g of fat/kg/day. In critically ill patients, the lipid content should not exceed 1g/kg/day. These lipid emulsions are isotonic and can be delivered simultaneously with the protein and carbohydrate mixture in a 3-liter bag over a 24-hour infusion. **In general, 30% to 50% of nonprotein calories should be supplied in lipid form.** Serum triglyceride levels should be monitored to ensure that the patient can metabolize the fat.

- **Electrolytes, vitamins, and minerals.** In addition to calories and protein, nutritional support should be maintained in terms of electrolytes, vitamins, and trace elements. Daily maintenance requirements for electrolytes are as follows: sodium, 40 to 50 mEq; potassium, 30 to 40 mEq; magnesium, 8 to 10 mEq; calcium, 2 to 5 mEq; and phosphate, 13 to 25 mmol (19). A number of vitamins and trace elements must also be supplied to ensure that the patient is eumetabolic.

Fluid and Electrolytes

Water constitutes approximately 50% to 55% of the body weight of the average woman. Two thirds of this water is contained in the intracellular compartment. One third is contained in the extracellular compartment, of which one fourth is contained in plasma, and the remaining three fourths is in the interstitium.

Osmolarity, or tonicity, is a property derived from the number of particles in a solution. Sodium and chloride are the primary electrolytes contributing to the osmolarity of the extracellular compartment. Potassium and, to a lesser extent, magnesium and phosphate are the major intracellular electrolytes. Water flows freely between the intracellular and the extracellular spaces to maintain osmotic neutrality throughout the body. Any shifts in osmolarity in any fluid spaces within the body are accompanied by corresponding shifts in free water from spaces of lower to higher osmolarity, thus maintaining equilibrium.

The average adult daily fluid maintenance requirement is approximately 30 mL/kg per day, or 2,000 to 3,000 mL/day (21). This level is offset partially by insensible losses of 1,200 mL/day, which include losses from the lungs (600 mL), skin (400 mL), and gastrointestinal tract (200 mL). Urinary output from the kidney accounts for the

remainder of the fluid loss, and this output will vary depending on total body intake of water and sodium. Approximately 600 to 800 mOsm of solute are excreted by the kidney daily. Healthy kidneys can concentrate urine up to approximately 1,200 mOsm and, therefore, the minimum output can range between 500 and 700 mL/day. The maximal urine output of the kidney can be as high as 20 L/day, as seen in patients with diabetes insipidus. In healthy individuals, the kidney adjusts output commensurate with daily fluid intake.

The major extracellular buffer used in the acid-base balance is the bicarbonate-carbonic acid system: $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^-$ (22). Typically, the body will maintain a bicarbonate-to-carbonic acid ratio of 20:1 to maintain an extracellular pH

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of 7.4. Both the lung and the kidney play integral roles in the maintenance of normal extracellular pH via retention or excretion of carbon dioxide and bicarbonate. Under conditions of alkalosis, minute ventilation decreases and renal excretion of bicarbonate increases to restore the normal ratio of bicarbonate to carbonic acid; the opposite occurs with acidosis.

Ultimately, the kidney plays the most important role in fluid and electrolyte balance through excretion and retention of water and solute. Circulating antidiuretic hormone and aldosterone help modulate the process. Serum osmolarity affects hypothalamic release of antidiuretic hormone and aldosterone secretion in response to renal perfusion. Under states of dehydration or hypovolemia, serum antidiuretic hormone levels increase, leading to increased resorption of water in the distal tubule of the kidney. In addition, increased aldosterone release promotes increased sodium and water retention. The opposite occurs in states of fluid excess. As a result, individuals with normal renal function and circulating antidiuretic hormone and aldosterone levels maintain normal serum osmolarity and electrolyte composition, despite daily fluctuations of fluid and electrolyte intake.

Various disease states can alter the normal fluid and electrolyte homeostatic mechanisms, making perioperative fluid and electrolyte management more difficult. Patients with intrinsic renal disease are unable to excrete solute and to maintain acid-base balance. In patients undergoing the stress of chronic starvation or severe illness, there may be an inappropriately high level of circulating antidiuretic hormone and aldosterone, resulting in fluid and sodium retention. With severe cardiac disease, secondary renal hypoperfusion can lead to increased aldosterone synthesis and, therefore, increased sodium and water retention by the

kidney. Finally, patients with severe diabetes can have significant osmotic diuresis as well as acid-base dysfunction secondary to circulating keto acids. Treatment of renal, cardiac, or endocrine disorders preoperatively is imperative and often will rectify fluid and electrolyte abnormalities.

Special attention is warranted in the elderly patient undergoing surgery.

Normal physiological changes associated with aging can increase the likelihood of fluid and electrolyte disorders. These changes include decreased glomerular filtration rate, decreased urinary concentrating ability, and narrowed limits for excretion of water and electrolytes (23). Fluid and electrolyte management in the preoperative and perioperative periods requires knowledge of the daily fluid and electrolyte requirements for maintenance, replacement of ongoing fluid and electrolyte losses, as well as correction of any existing abnormalities.

Fluid and Electrolyte Maintenance Requirements

The body adjusts to higher and lower volumes of intake by changes in plasma tonicity. Alterations in plasma tonicity induce adjustments in circulating antidiuretic hormone levels, which ultimately regulate the amount of water retained in the distal tubule of the kidney. In the preoperative and the early postoperative periods, it is usually only necessary to replace sodium and potassium. Chloride is automatically replaced, concomitant with sodium and potassium, because chloride is the usual anion used to balance sodium and potassium in electrolyte solutions. There are various commercially available solutions containing 40 mmol of sodium chloride, with smaller amounts of potassium, calcium, and magnesium, designed to meet the requirements of a patient who is receiving 3 L of intravenous fluids per day. **The daily requirement, however, can be met by any combination of intravenous fluids. For example, 2 L of D5 (5% dextrose)/0.45 normal saline (7 mEq sodium chloride each), supplemented with 20 mEq of potassium chloride, followed by 1 liter of D5W (5% dextrose in water) with 20 mEq of potassium chloride, would suffice.**

Fluid and Electrolyte Replacement

Fluid and electrolyte losses beyond the daily average must be replaced by appropriate solutions. The choice of solutions for replacement depends on the composition of the fluids lost. Often, it

is difficult to measure free water loss, particularly in patients who

have high losses from the lungs, skin, or the gastrointestinal tract. Weighing these patients daily can be very useful. Up to 300 g of weight loss daily can be attributable to weight loss from catabolism of protein and fat in the patient who is taking nothing by mouth (21). Any loss beyond this level, however, represents fluid loss, which should be replaced accordingly.

Patients with a high fever can have increased pulmonary and skin loss of free water, sometimes in excess of 2 to 3 L/day. These losses should be replaced with free water in the form of D5W. Perspiration typically has one third the osmolarity of plasma and can be replaced with D5W or, if the loss is excessive, with D5/0.25 normal saline.

Patients with acute blood loss need replacement with appropriate isotonic fluid or blood or both. There is a wide range of plasma volume expanders, including albumin, dextran, and hetastarch solutions, that contains large-molecular-weight particles (< 50 kilodaltons (kDa) molecular weight). These particles are slow to exit the intravascular space, and about one half of the particles remain after 24 hours. Controversy exists over the ideal strategy for intravascular volume replacement (24). Meta-analyses on the use of human albumin and crystalloids versus colloids in fluid resuscitation have not shown a benefit in mortality rates (25,26). However, caution is required in interpreting results from these pooled controlled trials because mortality outcome was not the end point of most of the studies, and publication bias is a limitation. Possible side effects with synthetic colloid solutions include adverse effects on hemostasis, severe anaphylactic reactions, and impairment of renal function (24). These solutions are expensive, however, and **for most cases, simple replacement with 0.9 normal saline or lactated Ringer's solution will suffice.** One third of the volume of lactated Ringer's solution or normal saline typically will remain in the intravascular space, and the remainder goes to the interstitium.

Appropriate replacement of gastrointestinal fluid loss depends on the source of fluid loss in the gastrointestinal tract. Gastrointestinal secretions beyond the stomach and up to the colon are typically isotonic with plasma, with similar amounts of sodium, slightly lower amounts of chloride, slightly alkaline pH, and more potassium (in the range of 10–20 mEq/L). Under normal conditions, stool is hypotonic. However, under conditions of increased flow (i. e., severe diarrhea), stool contents are isotonic with a composition similar to that of the small bowel contents. Gastric contents are typically hypotonic, with one third the sodium of

plasma, increased amounts of hydrogen ion, and low pH.

In patients who have gastric outlet obstruction, nausea, and vomiting, or who undergo nasogastric suction, appropriate replacement of gastric secretions can be provided with a solution such as D5/0.45 normal saline with 20 mEq/L of potassium. Potassium supplementation is particularly important to prevent hypokalemia in these patients, whose kidneys attempt to conserve hydrogen ions in the distal tubule of the kidney in exchange for potassium ions.

In patients with bowel obstruction, 1 to 3 L of fluid can be sequestered daily in the gastrointestinal tract. This fluid should be replaced with isotonic saline or lactated Ringer's solution. Similarly, patients with enterocutaneous fistulas or new ileostomies should receive replacement with isotonic fluids.

Correction of Existing Fluid and Electrolyte Abnormalities

Patients who have fluid or electrolyte abnormalities preoperatively can pose a diagnostic challenge. The correct diagnosis and therapy is contingent on a correct assessment of total body fluid and electrolyte status. The management of hyponatremia, for example, may be either fluid restriction or fluid replacement. The choice of treatment depends on whether there is overall extracellular fluid excess and normal body sodium stores or decreased overall total body sodium stores and extracellular fluid. A detailed history is necessary to disclose any underlying medical illness and to assess the amount and duration of any

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abnormal fluid losses or intake. Initial evaluation should include an assessment of hemodynamic, clinical, and urinary parameters to determine the overall level of hydration as well as the fluid status of the extracellular fluid compartment. The patient who has good skin turgor, moist mucosa, stable vital signs, and good urinary output is well hydrated. Nonpitting edema is indicative of extracellular fluid excess, whereas patients with orthostasis, sunken eyes, parched mouth, and decreased skin turgor clearly have extracellular volume contraction. A patient's overall extracellular fluid status does not always reflect the hydration status of the intravascular compartment, however. A patient can have increased interstitial fluid and yet be intravascularly dry, requiring replacement with isotonic fluid.

The laboratory workup for patients who may have pre-existing fluid problems should include assessment of blood hematocrit, serum chemistry, glucose, blood urea nitrogen (BUN) and creatinine, urine osmolarity, and urine electrolyte levels.

Serum osmolarity is mainly a function of the concentration of sodium and is given by the following equation:

$$2 \times \text{Na}^+ + \text{glucose (mg/dL)}/18 + \text{BUN (mg/dL)}/2.8$$

Normal serum osmolarity is typically 290 to 300 mOsm. Blood hematocrit will rise or fall inversely at a rate of 1% per 500-mL alteration of extracellular fluid volume. The BUN:creatinine ratio is typically 10:1 but will rise to a ratio of greater than 20:1 under conditions of extracellular fluid contraction. Under conditions of extracellular fluid deficit, urine osmolarity will typically be high (>400 mOsm), whereas urine sodium concentration is low (<15 mEq/L), indicative of an attempt by the kidney to conserve sodium. Under conditions of extracellular fluid excess or in cases of renal disease in which the kidney has impaired ability to retain sodium and water, urine osmolarity will be low and urine sodium will be high (>30 mEq/L). Finally, changes in sodium can give insight into the degree of extracellular fluid excess or deficit. In the average person, the serum sodium rises by 3 mmol/L for every liter of water deficit and falls by 3 mmol/L for each liter of water excess. One must be careful in making these estimates, however, because patients with prolonged water and electrolyte loss can have low serum sodium levels and marked water deficits.

Specific Electrolyte Disorders

Hyponatremia

Because sodium is the major extracellular cation, shifts in serum sodium levels are usually inversely correlated with the hydration state of the extracellular fluid compartment. The pathophysiology of hyponatremia, then, is usually expansion of body fluids leading to excess total body water (22,27). Symptomatic hyponatremia usually does not occur until the serum sodium is below 120 to 125 mEq/L. The severity of the symptoms (nausea, vomiting, lethargy, seizures) is related more to the rate of change of serum sodium than to the actual serum sodium level.

Hyponatremia in the form of extracellular fluid excess can be seen in patients with renal or

cardiac failure as well as in conditions such as nephrotic syndrome, in which total body salt and water are increased, with a relatively greater increase in the latter. Administration of hypertonic saline to correct the hyponatremia would be inappropriate in this setting. The treatment should include, in addition to correcting the underlying disease process, water restriction with diuretic therapy. Inappropriate secretion of antidiuretic hormone (ADH) can occur with head trauma, pulmonary or cerebral tumors, and states of stress. The abnormally elevated ADH results in excess water retention. Treatment includes water restriction

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and, if possible, correction of the underlying cause. *Demeclocycline* has been shown to be effective in this disorder via its action in the kidney.

Inappropriate replacement of body salt losses with water alone will result in hyponatremia. This situation will typically occur in patients who lose large amounts of electrolytes secondary to vomiting, nasogastric suction, diarrhea, or gastrointestinal fistulas, and who received replacement with hypotonic solutions. Simple replacement with isotonic fluids and potassium will usually correct the abnormality. Rarely, rapid correction of the hyponatremia is necessary, in which case hypertonic saline (3%) can be administered. Hypertonic saline should be administered very cautiously to avoid a rapid shift in serum sodium, which will induce central nervous system dysfunction.

Hypernatremia

Hypernatremia is an uncommon condition that can be life-threatening if severe (serum sodium greater than 160 mEq/L). The pathophysiology is extracellular fluid deficit. The resultant hyperosmolar state leads to decreased water volume in cells in the central nervous system, which, if severe, can cause disorientation, seizures, intracranial bleeding, and death. The causes include excessive extrarenal water loss, which can occur in patients who have a high fever, have undergone tracheostomy in a dry environment, or have extensive thermal injuries; who have diabetes insipidus, either central or nephrogenic; and who have iatrogenic salt loading. The treatment involves correction of the underlying cause (correction of fever, humidification of the tracheostomy, administration of pitressin for control of central diabetes insipidus) and replacement with free water either by the oral route or intravenously with D5W. As with severe hyponatremia, marked hypernatremia should be

corrected slowly.

Hypokalemia

Hypokalemia may be encountered preoperatively in patients with significant gastro-intestinal fluid loss (prolonged emesis, diarrhea, nasogastric suction, intestinal fistulas) and marked urinary potassium loss secondary to renal tubular disorders (renal tubular acidosis, acute tubular necrosis, hyperaldosteronism, prolonged diuretic use). It can also arise from prolonged administration of potassium-free parenteral fluids in patients who are restricted from ingesting anything by mouth. The symptoms associated with hypokalemia include neuromuscular disturbances, ranging from muscle weakness to flaccid paralysis, and cardiovascular abnormalities, including hypotension, bradycardia, arrhythmias, and enhancement of digitalis toxicity. These symptoms rarely occur unless the serum potassium level is less than 3 mEq/L. The treatment is potassium replacement. Oral therapy is preferable in patients who are on an oral diet. If necessary, potassium replacement can be given intravenously in doses that should not exceed 10 mEq/hour.

Hyperkalemia

Hyperkalemia is encountered infrequently in preoperative patients. It is usually associated with renal impairment but can also be seen in patients who have adrenal insufficiency, are taking potassium-sparing diuretics, and have marked tissue breakdown such as that occurring with crush injuries, massive gastrointestinal bleeding, or hemolysis. The clinical manifestations are mainly cardiovascular. Marked hyperkalemia (potassium greater than 7 mEq/L) can result in bradycardia, ventricular fibrillation, and cardiac arrest. The treatment chosen depends on the severity of the hyperkalemia and whether there are associated cardiac abnormalities detected with electrocardiography. *Calcium gluconate* (10 mL of a 10% solution), given intravenously, can offset the toxic effects of hyperkalemia on the heart. One ampule each of sodium bicarbonate and D50, with or without insulin, will cause a rapid shift of potassium into cells. Over the longer term, cation exchange resins such as *sodium polystyrene sulfate* (*Kayexalate*), taken orally

or by enema, will bind and decrease total body potassium. Hemodialysis is reserved for emergent conditions in which other measures are not sufficient or have failed.

Postoperative Fluid and Electrolyte Management

Several hormonal and physiologic alterations in the postoperative period may complicate fluid and electrolyte management. The stress of surgery induces an inappropriately high level of circulating ADH. Circulating aldosterone levels also are increased, especially if sustained episodes of hypotension have occurred either intraoperatively or postoperatively. The elevated levels of circulating ADH and aldosterone make patients prone to sodium and water retention postoperatively.

Total body fluid volume may be altered significantly postoperatively. First, 1 mL of free water is released for each gram of fat or tissue that is catabolized and, in the postoperative period, several hundred milliliters of free water is released daily from tissue breakdown, particularly in the patient who has undergone extensive intra-abdominal dissection and who is restricted from ingesting food and fluids by mouth. This free water is often retained in response to the altered levels of ADH and aldosterone. Second, fluid retention is further enhanced by third spacing, or sequestration of fluid in the surgical field. **The development of an ileus may result in an additional 1 to 3 L of fluid per day being sequestered in the bowel lumen, bowel wall, and peritoneal cavity.**

In contrast to renal sodium homeostasis, the kidney lacks the capacity for retention of potassium. **In the postoperative period, the kidneys will continue to excrete a minimum of 30 to 60 mEq/L of potassium daily, irrespective of the serum potassium level and total body potassium stores (22).** If this potassium loss is not replaced, hypokalemia may develop. Tissue damage and catabolism during the first postoperative day usually result in the release of sufficient intracellular potassium to meet the daily requirements. However, beyond the first postoperative day, potassium supplementation is necessary.

Correct maintenance of fluid and electrolyte balance in the postoperative period starts with the preoperative assessment, with emphasis on establishing normal fluid and electrolyte parameters before surgery. Postoperatively, close monitoring of daily weight, urine output, serum hematocrit, serum electrolytes, and hemodynamic parameters will yield the necessary information to make correct adjustments in crystalloid replacement. The

normal daily fluid and electrolyte requirements must be met and any unusual fluid and electrolyte losses, such as from the gastrointestinal tract, lungs, or skin, must be replaced. After the first few postoperative days, third-space fluid begins to mobilize back into the intravascular space, and ADH and aldosterone levels revert to normal. The excess fluid retained perioperatively is thus mobilized and excreted through the kidneys, and exogenous fluid requirements decrease. Patients with inadequate cardiovascular or renal reserve are prone to fluid overload during this time of third-space reabsorption, especially if intravenous fluids are not appropriately reduced.

The most common fluid and electrolyte disorder in the postoperative period is fluid overload. The fluid excess can occur concomitantly with normal or decreased serum sodium. Large amounts of isotonic fluids are usually infused intraoperatively and postoperatively to maintain blood pressure and urine output. Because the infused fluid is often isotonic with plasma, it will remain in the extracellular space. Under such conditions, serum sodium will remain within normal levels. Fluid excess with hypotonicity (decreased serum sodium) can occur if large amounts of isotonic fluid losses (e.g., blood and gastrointestinal tract) are inappropriately replaced with hypotonic fluids. Again, the predisposition toward retention of free water in the immediate postoperative period compounds the problem. An increase in body weight occurs concomitantly with the fluid expansion. In the patient who is not allowed anything by mouth, catabolism should induce a daily weight loss as great as 300 g/day. Clearly, the patient who is gaining weight in excess of 150 g/day

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is in a state of fluid expansion. Simple fluid restriction will correct the abnormality. When necessary, diuretics can be used to increase urinary water excretion.

States of fluid dehydration are uncommon but will occur in patients who have large daily fluid losses that are not replaced. **Gastrointestinal losses should be replaced with the appropriate fluids. Patients with high fevers should be given appropriate free water replacement, because up to 2 L/day of free water can be lost through perspiration and hyperventilation.** Although these increased losses are difficult to monitor, a reliable estimate can be obtained by monitoring body weight.

Postoperative Acid-Base Disorders

A variety of metabolic, respiratory, and electrolyte abnormalities in the postoperative period can result in an imbalance in normal acid-base homeostasis, leading to alkalosis or acidosis. Changes in the respiratory rate will directly affect the amount of carbon dioxide that is exhaled. **Respiratory acidosis will result from carbon dioxide retention in patients who have hypoventilation from central nervous system depression.** This condition can result from oversedation with narcotics, particularly in the presence of concurrent severe chronic obstructive pulmonary disease. **Respiratory alkalosis can result from hyperventilation caused by excitation of the central nervous system by drugs, pain, or excess ventilator support.** Numerous metabolic derangements can result in *alkalosis* or *acidosis*. Proper fluid and electrolyte replacement as well as maintenance of adequate tissue perfusion will help prevent most acid-base disorders that occur during the postoperative period.

Alkalosis

The most common acid-base disorder encountered in the postoperative period is alkalosis (22). Alkalosis is usually of no clinical significance and resolves spontaneously. Several etiologic factors may include hyperventilation associated with pain; posttraumatic transient hyperaldosteronism, which results in decreased renal bicarbonate excretion; nasogastric suction, which removes hydrogen ions; infusion of bicarbonate during blood transfusions in the form of citrate, which is converted to bicarbonates; administration of exogenous alkali; and use of diuretics. Alkalosis can usually be corrected easily with removal of the inciting cause, as well as with correction of extracellular fluid and potassium deficits (Table 20.2). Full correction can usually be safely achieved over 1 to 2 days.

Table 20.2 Causes of Metabolic Acidosis

<i>Disorder</i>	<i>Source of Alkali</i>	<i>Cause of Renal HCO Retention</i>
<i>Gastric alkalosis</i>	Gastric mucosa	↓↓ECF, ↓K
Nasogastric suction		
Vomiting		
<i>Renal alkalosis</i>		
Diuretics	Renal epithelium	↓ECF, ↓K
Respiratory acidosis and diuretics		↓ECF, ↓K, ↑PCO ₂
<i>Exogenous base</i>	NaHCO ₃ , Na citrate, Na lactate	Coexisting disorder of ECF, K, PaCO ₂
↓ECF, extracellular fluid depletion; ↓K, potassium depletion; ↑↑PCO ₂ , carbon dioxide retention; NaHCO ₃ , sodium bicarbonate; PaCO ₂ , partial pressure of carbon dioxide, arterial.		

Marked alkalosis, with serum pH higher than 7.55, can result in serious cardiac arrhythmias or central nervous system seizures. Myocardial excitability is particularly

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pronounced with concurrent hypokalemia. Under such conditions, fluid and electrolyte replacement may not be sufficient to correct the alkalosis rapidly. *Acetazolamide* (250–500 mg), can be given orally or intravenously 2 to 4 times daily to induce renal bicarbonate diuresis. Treatment with an acidifying agent is rarely necessary and should be reserved for acutely symptomatic patients (i.e., those with cardiac or central nervous system dysfunction) or for patients with advanced renal disease. Under such conditions, *hydrogen chloride* (5–10 mEq/hour of a 100-mmol solution) can be given via a central intravenous line. *Ammonium chloride* can also be given orally or intravenously but should not be given to patients with hepatic disease.

Acidosis

Metabolic acidosis is less common than alkalosis during the postoperative period, but acidosis can potentially be serious because of its effect on the cardiovascular system. Under conditions of acidosis, there are decreased myocardial contractility, a propensity for vasodilation of the peripheral vasculature leading to hypotension, and refractoriness of

the fibrillating heart to defibrillation (22). These effects promote decompensation of the cardiovascular system and can hinder attempts at resuscitation.

Metabolic acidosis results from a decrease in serum bicarbonate levels caused by the consumption and replacement of bicarbonate by circulating acids or the replacement by other anions such as chloride. The proper workup includes a measurement of the anion gap:

$$\text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-) = 10 \text{ to } 14 \text{ mEq/L (normal)}$$

The anion gap is also composed of circulating protein, sulfate, phosphate, citrate, and lactate (28).

With metabolic acidosis, the anion gap can be increased or normal. An increase in circulating acids will consume and replace bicarbonate ion, thus increasing the anion gap. The causes include an increase in circulating lactic acid secondary to anaerobic glycolysis, such as that seen under conditions of poor tissue perfusion; increased ketoacids, as with cases of severe diabetes or starvation; exogenous toxins; and renal dysfunction, which leads to increased circulating sulfates and phosphates (29). The diagnosis can be established via a thorough history and measurement of serum lactate (normal <2 mmol/L), serum glucose, and renal function parameters. Metabolic acidosis in the face of a normal anion gap is usually the result of an imbalance of the ions chloride and bicarbonate, which occurs under conditions leading to excess chloride and decreased bicarbonate. Hyperchloremic acidosis can be seen in patients who have undergone saline loading. Bicarbonate loss will be seen in patients with small bowel fistulas, new ileostomies, severe diarrhea, or renal tubular acidosis. Finally, in patients with marked extracellular volume expansion, which often occurs postoperatively, the relative decrease in serum sodium and bicarbonate will result in a mild acidosis. A summary of the various causes of metabolic acidosis is shown in Table 20.3.

Table 20.3 Causes of Metabolic Acidosis

High Anion Gap	Normal Anion Gap	
	Hyperkalemic	Hypokalemic
Uremia	Hyporeninism	Diarrhea
Ketoacidosis	Primary adrenal failure	Renal tubular acidosis
Lactic acidosis	NH ₂ Cl	Ileal and sigmoid bladders
<i>Aspirin</i>	Sulfur poisoning	Hyperalimentation
Paraldehyde	Early chronic renal failure	
Methanol	Obstructive uropathy	
Ethylene glycol		
Methyl malonic aciduria		
NH ₂ Cl (chloramine)		

Adapted from **Narins RG, Lazarus MJ**. Renal system. In: **Vandam LD**, ed. *To make the patient ready for anesthesia: medical care of the surgical patient*, 2nd ed. Menlo Park, CA: Addison Wesley, 1984:67–114.

The treatment of metabolic acidosis depends on the cause. In patients with lactic acidosis, restoration of tissue perfusion is imperative. This state can be accomplished through cardiovascular and pulmonary support as needed, oxygen therapy, and aggressive treatment of systemic infection wherever appropriate. Ketosis from diabetes can be corrected gradually with *insulin* therapy. Ketosis resulting from chronic starvation or from lack of caloric support postoperatively can be corrected with nutrition. In patients with normal anion gap acidosis, bicarbonate losses from the gastrointestinal tract should be replaced, excess chloride administration can be curtailed and, where necessary, a loop diuretic can be used to induce renal clearance of chloride. Dilutional acidosis can be corrected with mild fluid restriction.

Bicarbonates should not be given unless serum pH is lower than 7.2 or severe cardiac complications secondary to acidosis are present. Furthermore, close monitoring of serum potassium levels is mandatory. Under states of acidosis, potassium will exit the cell and enter the circulation. The patient with a normal potassium concentration and metabolic acidosis is actually depleted of intracellular potassium. Treatment of the acidosis without potassium replacement will result in severe hypokalemia with its associated risks. A summary of

the various acid-base abnormalities and associated therapies is shown in Table 20.4.

Table 20.4 Acid-Base Disorders and Their Treatment				
Primary Disorder	Defect	Common Causes	Compensation	Treatment
<i>Respiratory acidosis</i>	Carbon dioxide (hypoventilation)	Central nervous system depression Airway and lung impairment	Renal excretion of acid salts Bicarbonate retention dioxide production Chloride shift into red blood cells	Restoration ventilation Control of excess
<i>Respiratory alkalosis</i>	Hyperventilation	Central nervous system excitation Excess ventilator support	Renal excretion of sodium, potassium bicarbonate Absorption of hydrogen and chloride ions Lactate release from red blood cells	Correction hyperventilation
<i>Metabolic acidosis</i>	Excess loss of base Increased nonvolatile acids	Excess chloride versus sodium Increased bicarbonate loss Lactic, ketoacidosis Uremia Dilution acidosis	Respiratory alkalosis Renal excretion of hydrogen and chloride ions Resorption of potassium bicarbonate	Increase sodium load give bicarbonate for pH < 7.2 Restore buffers, protein, hemoglobin

<i>Metabolic acidosis</i>	Excess loss of chloride and potassium Increased bicarbonate	Gastrointestinal losses of chloride Excess intake of bicarbonate Diuretics Hypokalemia Extracellular fluid volume contraction	Respiratory acidosis May be hypoxia Renal excretion of bicarbonate and potassium Absorption of hydrogen and chloride ions	Increased chloride content Potassium replacement Acetazolamide (Diamox) to waste bicarbonate Vigorous volume replacement Occasional 0.1 NaHCl as needed
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NaHCl, sodium hydrochloride.

Perioperative Pain Management

Although satisfactory analgesia is easily achievable with currently available methods, patients continue to suffer unnecessarily from postoperative pain. Studies have consistently shown that 30% to 40% of patients suffer moderate to severe pain in the postoperative period (30,31). There are several reasons for the existing inadequacies in pain management. First, patient expectations of pain relief are low and they are not aware of the extent of analgesia that they should expect. In a study of the perception of pain relief after surgery, 86% of patients had moderate to severe pain after surgery, but 70% felt that the pain was as severe as they had expected (32). Second, there is a lack of formal physician training in pain management. This lack is epitomized by the commonly written order prescribing a range of narcotic to be given intramuscularly every 3 to 4 hours as needed, leaving pain management decisions to the nursing staff, with no attempt made to titrate the dose of the prescribed narcotic commensurate with individual patient requirements. Third, attitudes continue to be influenced by the common misconception that the use of narcotics in the postoperative period can result in opioid dependence. In one review, 20% of nurses responding to a staff questionnaire expressed concern that the use of opioid analgesics during the postoperative period could cause addiction (32). Studies have confirmed that nurses will administer less than one fourth of the total dose of narcotic that is prescribed on an as-needed basis. To facilitate acute pain management and reduce the number of adverse outcomes, the American Society of Anesthesiologists has established practice guidelines for acute

pain management in the perioperative setting (33).

The *minimal effective analgesic concentration (MEAC)* refers to the serum concentration of a drug below which very little analgesia is achieved. At the MEAC, receptor and plasma concentrations of a drug are in equilibrium. Steady-state drug concentrations above the MEAC are difficult to achieve with intramuscular depot injection (34). In one study, patients receiving intramuscular injections with *meperidine hydrochloride (Demerol)* every 4 hours experienced marked inpatient and interpatient variations in

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narcotic drug peak concentrations as well as in the time required to reach these peaks. As a result, serum concentrations of drug were above the MEAC an average of only 35% of each 4-hour dosing interval (35). Variable pain control following intermittent intramuscular injections is the result of inadequate, highly variable, and unpredictable blood concentrations (36).

Adequate analgesia can be achieved through intramuscular or subcutaneous modes of administration, but unpredictable absorption can make titration difficult. Small intravenous boluses can be more easily titrated but may be shorter acting, requiring more frequent injections and thus intensive nursing care, whereas larger intravenous boluses may be associated with a higher incidence of central nervous system and respiratory depression.

The *patient-controlled analgesia (PCA) technique*, which allows patients to self-administer small doses of narcotic on demand, allows titration of measured boluses of narcotic as needed to relieve pain. This technique can provide a more thorough analgesia with maintenance of steady-state drug concentrations above the MEAC.

Irrespective of the route of administration, analgesics must be front loaded to provide prompt analgesia from the start. Without front loading, attainment of the MEAC will not occur for at least three elimination half-lives of the narcotic agent that is used. After front loading, additional small boluses of narcotic can be administered until analgesia is achieved. From the total dose of drug required to achieve analgesia, maintenance drug dosages can then be determined and administered either as a continuous infusion or on a

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scheduled basis, so that the dose of drug administered offsets the amount that is cleared. Thereafter, prescribed doses of narcotic can be adjusted as needed.

Patient-controlled Analgesia

Devices for administering PCA are electronically controlled infusion pumps that deliver a preset dose of narcotic into a patient's indwelling intravenous catheter upon patient request. The devices all contain delay intervals or lockout times during which patient demands for more narcotic are not met. **These devices eliminate the delay between the onset of pain and the administration of analgesic agents, a common problem inherent with on-demand analgesic orders in busy hospital wards.** Patient-controlled analgesia has enjoyed excellent patient acceptance. Compared with conventional intramuscular injections, serum narcotic levels have significantly lower variability in patients using PCA (34). Patients using PCA have been shown to have improved analgesia, a lower incidence of postoperative pulmonary complications, and less confusion than those given intramuscular narcotics (37). Furthermore, the total dose of narcotic used has been lower with PCA than with conventional intramuscular depot injection.

The use of PCA does not by any means eliminate the adverse side effects of narcotics. Potentially life-threatening respiratory depression is seen in as many as 0.5% of patients using PCA. The use of a continuous narcotic infusion in addition to demand dosing has been associated with a fourfold increase in respiratory depression. Elderly patients and those with pre-existing respiratory compromise also are at risk for respiratory depression (34).

Carefully supervised regimens using continuous infusions, on-demand intramuscular therapy, or fixed dosage schedules (every-4-hour dosing) with on-demand supplementation can have analgesic efficacy comparable with PCA. Nonetheless, the type of close supervision required to achieve adequate on-demand analgesia without PCA is difficult to maintain. **Use of PCA shortens the time between the onset of pain and the administration of pain medication, provides more continuous access to analgesics, and allows for an overall steadier state of pain control.**

Epidural and Spinal Analgesia

Anesthetics and narcotics administered either in the epidural space or intrathecally are among the most potent analgesic agents available; the efficacy of these agents is greater than that provided by intravenous PCA techniques. These drugs can be administered in one of several ways, including a single-shot dose given by epidural or intrathecal injection,

intermittent injection given either on schedule or on demand, and continuous infusion.

Because of the risk of central nervous system infections and headaches, intrathecal administration is usually limited to a single dose of narcotic, local anesthetic, or both. In comparison with epidural administration, duration of action for a single dose is increased via the intrathecal route as a result of the high concentrations of drug attained in the cerebrospinal fluid. However, the risk of central nervous system and respiratory depression, as well as systemic hypotension, also is increased. Even the low doses of opioids required for intrathecal analgesia have been associated with an increased risk of respiratory depression (38). Therefore, some investigators have warned against the use of intrathecal spinal analgesia outside the intensive care setting.

Epidural administration is the preferred approach and provides extended (greater than 24 hours) pain control during the postoperative period. Relative contraindications are the presence of coagulopathy, sepsis, and hypotension. Both anesthetic and narcotic agents have been used with excellent efficacy. Among the anesthetic agents, *bupivacaine* has been the most popular, providing excellent analgesia with minimal toxicity. Epidural analgesia is most suited for pain control in the lower abdomen and extremities. Potential adverse effects of epidural anesthetic agents include urinary retention, motor weakness,

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hypotension, and central nervous system and cardiac depression. In contrast to anesthetic agents, opioids offer excellent analgesia without accompanying sympathetic blockade. Epidural opioids tend to have a much longer duration of action, and hypotension is a rare complication. Compared with epidural anesthetics, however, there is a higher incidence of nausea and vomiting, respiratory depression, and pruritus (39).

Compared with analgesics administered intramuscularly or intravenously, epidural analgesia has been shown to be associated with improved pulmonary function postoperatively, a lower incidence of pulmonary complications, a decrease in postoperative venous thromboembolic complications (most likely secondary to earlier ambulation), fewer gastrointestinal side effects, a lower incidence of central nervous system depression, and shorter convalescence (39). **A recent systematic review concluded that continuous epidural anesthesia is more effective than intravenous opioid PCA in reducing postoperative pain for up to 72 hours after abdominal surgery** (40).

Severe respiratory depression, which occurs in less than 1% of patients, is the most serious potential complication. A lower incidence of respiratory depression occurs with the

more lipophilic drugs such as *fentanyl*, which is quickly absorbed within the spinal cord and is, therefore, less likely to diffuse to the central nervous system respiratory control centers. Pruritus, nausea, and urinary retention are common but can be managed easily and usually are of little clinical significance. Cost is perhaps the main and most limiting drawback of epidural analgesia.

Close monitoring by nursing staff is required for safe administration of epidural analgesia. However, an intensive care setting is not necessary. Epidural analgesics can be administered safely in a hospital ward setting under close nursing supervision, using respiratory monitoring with hourly ventilatory checks during the first 8 hours of epidural analgesia.

Nonsteroidal Anti-inflammatory Drugs

Current therapeutic strategies for perioperative pain control are largely dependent on multimodal therapy with opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). The nonselective NSAID *ketorolac* is a potent drug that can be given orally or parenterally. ***Ketorolac has a slightly slower onset of activity than fentanyl but has an analgesic potency comparable to morphine.*** The theoretical advantages of NSAIDs over opioids include absence of respiratory depression, lack of abuse potential, decreased sedative effects, decreased nausea, early return of bowel function, and faster recovery. In clinical studies, *ketorolac* has been found to have analgesic effects similar to those of morphine in postoperative orthopedic patients and, when used in conjunction with PCA, significantly reduced opioid requirements (41,42). Depending on the type of surgery, *ketorolac* has an opioid dose-sparing effect of a mean of 36% and improves analgesic control of moderate to severe pain 24 hours postoperatively (43). In the obstetric population, intravenous *ketorolac* is effective in reducing postoperative narcotic use after cesarean delivery (44). Although the U. S. Food and Drug Administrative has not approved *ketorolac* for use during lactation, it has been quantified in breast milk and has lower levels than *ibuprofen* (45).

Potential adverse effects associated with the use of NSAIDs include an increased risk of renal compromise (particularly in patients suffering from acute hypovolemia), gastrointestinal side effects, hypersensitivity reactions, and bleeding. The effects of *ketorolac* on bleeding have been inconsistent. Studies of *ketorolac* on healthy volunteers showed transient increases in bleeding time and decreases in platelet aggregation, but these changes were not clinically significant (46). A retrospective cohort study showed increased risk of gastrointestinal and

operative site bleeding in elderly patients receiving high doses of *ketorolac*, between 105 mg/day and 120 mg/day (47). In addition, increased risk for all gastrointestinal bleeding was associated with use of *ketorolac* for more than 5 days (47). Controlled prospective studies have not shown a significant increase in blood loss in patients who receive NSAIDs perioperatively. *Ketorolac* may be associated with elevated

rates of acute renal failure when therapy exceeds 5 days (48). A meta-analysis of the use of postoperative NSAIDs in patients with normal preoperative renal function showed a clinically insignificant reduction in renal function (49). Finally, these agents should be used with extreme care, if at all, in patients with asthma, because 5% to 10% of adult patients with asthma are sensitive to *aspirin* and other NSAID preparations.

With the potential advantage of less gastrointestinal toxicity, interest increased in the use of selective cyclooxygenase-2 (COX-2) inhibitors in perioperative pain management. However, in light of subsequent evidence showing increased incidence of serious cardiovascular events associated with COX-2 inhibitors, the use of these agents in the perioperative setting should be carefully assessed, especially in patients who have cardiovascular disease or who are at risk for it (50,51,52,53,54).

Antimicrobial Prophylaxis in Gynecologic Surgery

Gynecologic procedures often involve breaching of the reproductive and gastrointestinal tracts, which harbor endogenous flora capable of causing polymicrobial infections in the postoperative period. **Despite great advances in aseptic technique and drug development, bacterial contamination of the operative site and postoperative infections are an inevitable part of the practice of gynecologic surgery.** Prevention of these surgical complications includes using proper aseptic technique, minimizing tissue trauma, minimizing the amount foreign material in the surgical site, controlling diabetes, avoiding immunologic suppression, maximizing tissue oxygenation, draining blood and serum from the surgical site, and using prophylactic antibiotics. Antibiotic prophylaxis is given with the belief that antibiotics can enhance the immune mechanisms in the host tissues that would resist such infections by killing bacteria that inoculate the surgical site at the time of surgery (55).

Infections in the skin or pelvis that result from gynecologic surgery (e.g., parametritis, cuff cellulitis, pelvic abscess) typically are polymicrobial in nature. These infections are complex and often involve gram-negative rods, gram-positive cocci, and anaerobes (Table 20.5). Antibiotic prophylaxis should be sufficiently broad to cover these potential pathogens (56).

<i>Lactobacillus</i>	<i>Enterobacter agglomerans</i>
Diphtheroids	<i>Klebsiella pneumoniae</i>
<i>Staphylococcus aureus</i>	<i>Proteus mirabilis</i>
<i>Staphylococcus epidermidis</i>	<i>Proteus vulgaris</i>
<i>Streptococcus agalactiae</i>	<i>Morganella morganii</i>
<i>Streptococcus faecalis</i>	<i>Citrobacter diversus</i>
α -Hemolytic streptococci	<i>Bacteroides</i> species
Group D streptococci	<i>B. disiens</i>
Peptostreptococci	<i>B. fragilis</i>
<i>Peptococcus</i>	<i>B. melaninogenicus</i>
<i>Clostridium</i>	
<i>Gaffky anaerobia</i>	
<i>Escherichia coli</i>	
<i>Fusobacterium</i>	
<i>Enterobacter cloacae</i>	

The timing of antimicrobial prophylaxis is important. There is a relatively narrow window of opportunity for affecting outcomes (57). In the United States, it is customary to give antimicrobial prophylaxis shortly before or during the induction of anesthesia. **Data have revealed that a delay of 3 hours or more between the time of bacterial inoculation (i.e., skin incision) and administration of antibiotics may result in ineffective**

prophylaxis. Evidence indicates that for prophylaxis, one dose of antibiotic is appropriate. When the surgical procedure proceeds longer than 1 to 2 times the half-life of the drug or blood loss is greater than 1.5 liters, additional intraoperative doses of antibiotics should be administered to maintain adequate levels of medication in

serum and tissues. There are no data to support the continuation of prophylactic antimicrobial agents into the postoperative period for routine gynecologic procedures.

The cephalosporins have emerged as the most important class of antimicrobial agents for prophylaxis. These drugs have a broad spectrum and relatively low incidence of adverse reactions. *Cefazolin* (1 g) appears to be most widely used in the United States by gynecologic surgeons because of its relatively low cost and long half-life. Other cephalosporins such as *cefoxitin*, *cefotaxime*, and *cefotetan* also commonly are used for prophylaxis. These agents appear to have a broader spectrum of activity against anaerobic bacteria; however, there is little evidence to indicate that there is a clinically relevant distinction between *cefazolin* and the other agents.

Antimicrobial prophylaxis, although usually beneficial, is not without risk. Anaphylaxis is the most life-threatening complication from antibiotic use. Anaphylactic reactions to penicillins are reported to occur in 0.2% courses of treatment. The fatality rate is 0.0001%. Data indicate that it generally is safe to administer cephalosporins to women who report a history of adverse reactions to penicillins. The incidence of adverse reactions (e.g., skin flushing, itching) in women with a history of penicillin allergy who are given cephalosporins is 1% to 10%. The incidence of anaphylaxis in this setting is less than 0.02% (58).

A single dose of broad-spectrum antibiotics can result in pseudomembranous colitis, caused by *Clostridium difficile*. Diarrhea may develop in as many as 15% of hospitalized patients treated with beta-lactam antibiotics. In patients receiving *clindamycin*, the rate of diarrhea is nearly 30%. These gastrointestinal complications from antibiotics may cause serious morbidity in the surgical patient, and the surgeon should be familiar with recognizing and managing these problems (59).

Not all gynecologic surgery patients need to receive prophylactic antibiotics. The surgeon should choose agents to cover procedures based on available data, thereby avoiding the potential for adverse reactions and minimizing the unnecessary use of antibiotics, which may contribute to increased rates of antimicrobial resistance. In patients reporting adverse reactions to the aforementioned agents, other drugs or combinations should be chosen that will provide adequate prophylactic coverage. For example, *metronidazole* and *levofloxacin* or *clindamycin* and *gentamycin* are two alternative broad-spectrum prophylactic regimens that can be used patients undergoing hysterectomy to cover anaerobes, gram-positive cocci, and gram-negative rods (60). Some commonly used recommendations are listed in Table 20.6.

Table 20.6 Antibiotic Prophylaxis Regimens

Hysterectomy (vaginal/abdominal)	1 to 2 g IV <i>cefazolin</i> 2 g IV <i>cefoxitin</i> 1 to 2 g IV <i>cefotetan</i> 1 g IV <i>cefotaxime</i>
Hysterosalpingogram	100 mg <i>doxycycline</i> PO bid for 5 days
Abortion/dilation & curettage	100 mg <i>doxycycline</i> PO 1 hour before procedure, then 200 mg po after the procedure
Cervical conization	No clear recommendations; <i>doxycycline</i> suggested by some authors
Colporrhaphy	No clear recommendations, cephalosporins suggested by some authors
Laparoscopy (clean)	None
Laparotomy (clean)	None
Hysteroscopy	None
IV, intravenous; PO, by mouth; bid, twice daily.	

Subacute Bacterial Endocarditis Prophylaxis

Often, the gynecologic surgeon encounters the issue of endocarditis prophylaxis. Most commonly, a woman will report a history of a murmur or mitral valve prolapse to the surgeon during the preoperative interview. Data clearly indicate that surgeons and dentists in the United States overtreat these women with prophylactic antibiotics meant to prevent endocarditis.

It appears that most patients who report these cardiac conditions are at no increased risk for endocarditis. For example, most patients with mitral valve prolapse or benign murmurs do not require endocarditis prophylaxis at the time of gynecologic surgery.

A thorough history and physical examination, coupled with a preoperative echocardiography and consultation with a cardiologist, will provide a detailed assessment of the risk of endocarditis in these patients. The American Heart Association (AHA) has published guidelines for physicians and dentists to use in selecting patients and procedures for endocarditis prophylaxis. If the surgeon is uncertain, consultation with a cardiologist is appropriate. If it appears that the patient would benefit from endocarditis

prophylaxis, based on the cardiac lesion and the procedure she will undergo, the risk is stratified as high or moderate. **High-risk patients should receive *ampicillin* or *vancomycin* plus *gentamycin* in a multidose regimen. Moderate-risk patients receive *amoxicillin* or *ampicillin* or *vancomycin* as prophylaxis in a single-dose regimen. Of note, low-risk patients require no subacute bacterial endocarditis (SBE) prophylaxis regardless of the procedure.**

Antibiotics administered to prevent surgical site infection are not sufficient for endocarditis prophylaxis; however, some experts feel that antibiotics given for endocarditis prophylaxis may provide adequate coverage against postoperative infections. This claim may be suspect, however, in patients undergoing gynecologic surgery. Some of the regimens (e.g., single-dose oral *amoxicillin*) prescribed for endocarditis prophylaxis in some patients may not provide adequate coverage for flora (gram-negative rods and anaerobes) found in the reproductive or gastrointestinal tracts. The AHA guidelines provide detailed dosing and schedule information for endocarditis prophylaxis (Table 20.7) (61).

Table 20.7 Recommendations for Prophylaxis of Bacterial Endocarditis for Genitourinary and Gastrointestinal Procedures

<i>High-Risk Patients</i>	<i>Agents</i>	<i>Regimen</i>
Standard regimen	<i>Ampicillin</i> and	2.0 g IM or IV within 30 min of starting procedure; 1.0 g IM or IV 6 hr later
	<i>Gentamicin</i>	1.5 mg/kg (not to exceed 120 mg) within 30 min of starting procedure
Penicillin-allergic	<i>Vancomycin</i> and	1.0 g IV over 1–2 h completed within 30 min of starting procedure
	<i>Gentamicin</i>	1.5 mg/kg (not to exceed 120 mg) within 30 min of starting procedure
<i>Moderate-Risk Patients</i>	<i>Agents</i>	<i>Regimen</i>
Standard regimen	<i>Ampicillin</i> or	2.0 g IM or IV within 30 min of starting procedure
	<i>Amoxicillin</i>	2.0 g orally 1 h before procedure
Penicillin-allergic	<i>Vancomycin</i>	1.0 g IV over 1–2 h completed within 30 min of starting procedure

IM, intramuscularly; IV, intravenously.

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Postoperative Infections

Infections are a major source of morbidity in the postoperative period. Risk factors for infectious morbidity include the absence of perioperative antibiotic prophylaxis, contamination of the surgical field from infected tissues or from spillage of large bowel contents, an immunocompromised host, poor nutrition, chronic and debilitating severe illness, poor surgical technique, and pre-existing focal or systemic infection. Sources of postoperative infection can include the lung, urinary tract, surgical site, pelvic side wall, vaginal cuff, abdominal wound, and sites of indwelling intravenous catheters. Early identification and treatment of infection will result in the best outcome for these potentially serious complications.

Although infectious morbidity is an inevitable complication of surgery, the incidence of infections can be decreased by the appropriate use of simple preventive measures.

In cases that involve transection of the large bowel, spillage of fecal contents inevitably occurs. A thorough preoperative mechanical and antibiotic bowel preparation in combination with systemic antibiotic prophylaxis will help decrease the incidence of postoperative

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pelvic and abdominal infections in these patients. The surgeon can further decrease the risk of postoperative infections by using meticulous surgical technique. Blood and necrotic tissue are excellent media for the growth of aerobic and anaerobic organisms. In cases in which there is higher-than-usual potential for serum and blood to collect in spaces that have been contaminated by bacterial spill, closed-suction drainage may reduce the risk of infection. Antibiotic therapy, rather than prophylaxis, should be initiated during surgery in patients who have frank intra-abdominal infection or pus. Elective surgical procedures should be postponed in patients who have infections preoperatively. In an epidemiologic study conducted by the Centers for Disease Control and Prevention, the incidence of nosocomial surgical infections ranged from 4.3% in community hospitals to 7% in municipal hospitals (62). Urinary tract infections accounted for approximately 40% of these nosocomial infections. Infections of the

skin and wound accounted for approximately one third of the infections, and respiratory tract infections accounted for approximately 16%. In patients who had any type of infection before surgery, the risk of infection at the surgical wound site was increased fourfold. Rates of infection were higher in older patients, in patients with increased length of surgery, and in those with increased length of hospital stay before surgery. The relative risk was 3 times higher in patients with a community-acquired infection before surgery. These community-acquired infections included infections of the urinary and respiratory tracts.

Historically, the standard definition of febrile morbidity for surgical patients has been the presence of a temperature higher than or equal to 100.4°F (38°C) on two occasions at least 4 hours apart during the postoperative period, excluding the first 24 hours. However, other sources have defined fever as two consecutive temperature elevations greater than 101.0°F (38.3°C) (63,64). Febrile morbidity has been estimated to occur in as many as one half of patients; however, it is often self-limited, resolves without therapy, and is usually noninfectious in origin (65). Overzealous evaluations of postoperative fever, especially during the early postoperative period, are time consuming, expensive, and sometimes uncomfortable for the patient (64). **The value of 101.0°F is more useful than 100.4°F to distinguish an infectious cause from an inconsequential postoperative fever.**

The assessment of a febrile surgical patient should include a review of the patient's history with regard to risk factors. Both the history and the physical examination should focus on the potential sites of infection (Table 20.8). The examination should include inspection of the pharynx, a thorough pulmonary examination, percussion of the kidneys to assess for costovertebral angle tenderness, inspection and palpation of the abdominal incision, examination of sites of intravenous catheters, and an examination of the extremities for evidence of deep venous thrombosis or thrombophlebitis. In gynecologic patients, an appropriate workup may also include inspection and palpation of the vaginal cuff for signs of induration, tenderness, or purulent drainage. A pelvic examination should also be performed to identify a mass consistent with a pelvic hematoma or abscess and to look for signs of pelvic cellulitis.

Table 20.8 Posthysterectomy Infections

<i>Operative Site</i>	<i>Nonoperative Site</i>
Vaginal cuff	Urinary tract
Pelvic cellulitis	Asymptomatic bacteriuria
Pelvic abscess	Cystitis
Supervaginal, extraperitoneal	Pyelonephritis
Intraperitoneal	Respiratory
Adnexa	Atelectasis
Cellulitis	Pneumonia
Abscess	Vascular
Abdominal incision	Phlebitis
Cellulitis	Septic pelvic thrombophlebitis
Simple	
Progressive bacterial synergistic	
Necrotizing fasciitis	
Myonecrosis	

Patients with fever in the early postoperative period should have an aggressive pulmonary toilet, including incentive spirometry (64). If the fever persists beyond 72 hours postoperatively, additional laboratory and radiologic data may be obtained. The evaluation may include complete and differential white blood cell counts and a urinalysis. In one study, a routine urine culture had a yield of only 9%; therefore, cultures should not be analyzed unless indicated by the urinalysis results or symptoms (63). Routine chest radiography has a yield of 12.5% and should be performed in asymptomatic patients as well as those with signs and symptoms localizing to the lung (63). Blood cultures can also be obtained but will most likely be of little yield unless the patient has a high fever (102°F). In patients with costovertebral angle tenderness, IVP may be indicated to rule out the presence of ureteral damage or obstruction from surgery, particularly in the absence of laboratory evidence of urinary tract infection. Patients who have persistent fevers without a clear localizing source should undergo CT scanning of the abdomen and pelvis to rule out the presence of an intra-abdominal abscess. Finally, if fever persists in patients who have had gastrointestinal surgery, a barium enema or upper gastrointestinal studies with small bowel assessment may be indicated late in the course of the first postoperative week to rule out an anastomotic leak or fistula.

Urinary Tract Infections

Historically, the urinary tract has been the most common site of infection in surgical patients (62). However, the incidence reported in the more recent gynecologic literature has been less than 4% (65,66). This decrease in urinary tract infections is most likely the result of increased perioperative use of prophylactic antibiotics. The incidence of postoperative urinary tract infection in gynecologic surgical patients not receiving prophylactic antibiotics has been confirmed to be as high as 40% (67), and **even a single dose**

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of perioperative prophylactic antibiotic has been shown to decrease the incidence of postoperative urinary tract infection from 35% to 4% (68).

Symptoms of a urinary tract infection may include urinary frequency, urgency, and dysuria. In patients with pyelonephritis, other symptoms include headache, malaise, nausea, and vomiting. A urinary tract infection is diagnosed on the basis of microbiology and has been defined as the growth of 10^5 organisms/mL of urine cultured. Most infections are caused by coliform bacteria, with *Escherichia coli* being the most frequent pathogen. Other pathogens include *Klebsiella*, *Proteus*, and *Enterobacter* species. *Staphylococcus* organisms are the causative bacteria in fewer than 10% of cases.

Despite the high incidence of urinary tract infections in the postoperative period, few of these infections are serious. Most are confined to the lower urinary tract, and pyelonephritis is a rare complication (69). Catheterization of the urinary tract, either intermittently or continuously with the use of an indwelling catheter, has been implicated as a main cause of urinary tract contamination (70). In fact, more than one million catheter-associated urinary tract infections occur yearly in the United States, and **catheter-associated bacteria remains the most common etiology of gram-negative bacteremia in hospitalized patients.**

Bacteria adhere to the surface of urinary catheters and grow within bile films, which appear to protect embedded bacteria from antibiotics, making treatment less effective. Therefore, the use of urinary tract catheters should be minimized. An indwelling catheter should be removed or replaced in a patient undergoing treatment for catheter-related infections.

The treatment of urinary tract infection includes hydration and antibiotic therapy. Commonly prescribed and effective antibiotics include *penicillin*,

sulfonamides, cephalosporins, fluoroquinolones, and nitrofurantoin. The choice of antibiotic should be based on knowledge of the susceptibility of organisms cultured at a particular institution. In some institutions, for example, more than 40% of *E. coli* strains are resistant to *ampicillin*. For uncomplicated urinary tract infections, an antibiotic that has good activity against *E. coli* should be given in the interim while awaiting results of the urine culture and sensitivity data.

Patients who have a history of recurrent urinary tract infections, those with chronic indwelling catheters (Foley catheters or ureteral stents), and those who have urinary conduits should be treated with antibiotics that will be effective against the less common urinary pathogens such as *Klebsiella* and *Pseudomonas*. Chronic use of *fluoroquinolones* for prophylaxis is not advised because these agents are notorious for inducing antibiotic-resistant strains of bacteria.

Pulmonary Infections

The respiratory tract is an uncommon site for infectious complications in gynecologic surgical patients. In one study only six cases of pneumonia occurred in more than 4,000 women who underwent elective hysterectomy (65). This low incidence is probably a reflection of the young age and good health status of gynecologic patients in general. In acute care facilities, pneumonia is a frequent hospital-acquired infection, particularly in elderly patients (71). Risk factors include extensive or prolonged atelectasis, preexistent COPD, severe or debilitating illness, central neurologic disease causing an inability to clear oropharyngeal secretions effectively, and nasogastric suction (71). In surgical patients, early ambulation and aggressive management of atelectasis are the most important preventive measures. The role of prophylactic antibiotics remains unclear.

A significant percentage (40%–50%) of cases of hospital-acquired pneumonia is caused by gram-negative organisms. These organisms gain access to the respiratory tract from the oral pharynx. Gram-negative colonization of the oral pharynx has been shown to be increased in patients in acute care facilities and has been associated with the presence

of nasogastric tubes, pre-existing respiratory disease, mechanical ventilation, tracheal intubation, and paralytic ileus as a result of microbial overgrowth in the stomach (72).

Interestingly, the use of antimicrobial drugs seems to significantly increase the frequency

of colonization of the oral pharynx with gram-negative bacteria.

A thorough lung examination should be included in the assessment of all febrile surgical patients. In the absence of significant lung findings, chest radiography is probably of little benefit in patients at low risk for postoperative pulmonary complications. In patients with pulmonary findings or with risk factors for pulmonary complications, chest radiography should be performed. A sputum sample should also be obtained for Gram stain and culture. The treatment should include postural drainage, aggressive pulmonary toilet, and antibiotics. The antibiotic chosen should be effective against both gram-positive and gram-negative organisms. In patients who are receiving assisted ventilation, the antibiotic spectrum should include drugs that are active against *Pseudomonas* organisms.

Phlebitis

Intravenous catheter-related infections are common; the reported incidence is 25% to 35% (73). The intravenous site should be inspected daily, and the catheter should be removed if there is any associated pain, redness, or induration. Unfortunately, phlebitis can occur even with close surveillance of the intravenous site. In one study, more than 50% of the cases of phlebitis became evident more than 12 hours after discontinuation of intravenous catheters (74). In addition, less than one third of patients had symptoms related to the intravenous catheter site 24 hours before the diagnosis of phlebitis.

Intravenous catheters should be inserted using sterile technique, and they should be changed frequently. The institution of intravenous therapy teams has decreased the incidence of phlebitis by as much as 50% (73). This decrease is related not so much to surveillance of the intravenous catheter site as it is to frequent changing of intravenous catheters. The incidence of catheter-related phlebitis increases significantly after 72 hours. Therefore, intravenous catheters should be changed at least every 3 days.

Phlebitis can be diagnosed based on the presence of fever, pain, redness, induration, or a palpable venous cord. Occasionally, suppuration will be present. Phlebitis is usually self-limited and resolves within 3 to 4 days. The treatment includes application of warm, moist compresses and prompt removal of any catheters from the infected vein. Antibiotic therapy with antistaphylococcal agents should be instituted for catheter-related sepsis. Excision or drainage of an infected vein rarely is necessary.

Wound Infections

The results of a prospective study of more than 62,000 wounds were revealing in regard to the epidemiology of wound infections (75). The wound infection rate varied markedly, depending on the extent of contamination of the surgical field. The wound infection rate for clean surgical cases (infection not present in the surgical field, no break in aseptic technique, no viscus entered) was lower than 2%, whereas the incidence of wound infections with dirty, infected cases was 40% or higher. Preoperative showers with *hexachlorophene* slightly lowered the infection rate for clean wounds, whereas preoperative shaving of the wound site with a razor increased the infection rate. A 5-minute wound preparation immediately before surgery was as effective as preparation for 10 minutes. The wound infection rate increased with the duration of preoperative hospital stay as well as with the duration of surgery. In addition, incidental appendectomy increased the risk of wound infection in patients undergoing clean surgical procedures. The study concluded that **the incidence of wound infections could be decreased by short preoperative hospital stays, hexa-chlorophene showers before surgery, minimizing shaving of the wound site, use of meticulous surgical technique, decreasing operative time as much as possible, bringing drains out through sites other than the wound, and dissemination of information to surgeons regarding their wound infection rates.** A program instituting

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these conclusions led to a decrease in the clean wound infection rate from 2.5% to 0.6% over an 8-year period. The wound infection rate in most gynecologic services has been lower than 5%, reflective of the clean nature of most gynecologic operations.

The symptoms of wound infection often occur late in the postoperative period, usually after the fourth postoperative day, and may include fever, erythema, tenderness, induration, and purulent drainage. Wound infections that occur on postoperative days 1 through 3 are generally caused by streptococcal and *Clostridia* infections. The management of wound infections is mostly mechanical and involves opening the infected portion of the wound above the fascia, with cleansing and debridement of the wound edges as necessary. Wound care, consisting of debridement and dressing changes 2 to 3 times daily with mesh gauze, will promote growth of granulation tissue, with gradual filling in of the wound defect by secondary intention. Clean, granulating wounds

can often be secondarily closed with good success, shortening the time required for complete wound healing.

The technique of delayed primary wound closure can be used in contaminated surgical cases to lower the incidence of wound infection. Briefly, this technique involves leaving the wound open above the fascia at the time of the initial surgical procedure. Vertical interrupted mattress sutures through the skin and subcutaneous layers are placed 3 cm apart but are not tied. Wound care is instituted immediately after surgery and continued until the wound is noted to be granulating well. Sutures may then be tied and the skin edges further approximated using sutures or staples. **Using this technique of delayed primary wound closure, the overall wound infection rate has been shown to be decreased from 23% to 2.1% in high-risk patients (76).**

Pelvic Cellulitis

Vaginal cuff cellulitis is present to some extent in most patients who have undergone hysterectomy. It is characterized by erythema, induration, and tenderness at the vaginal cuff. Occasionally, a purulent discharge from the apex of the vagina may also be present. The cellulitis is often self-limited and does not require any treatment. Fever, leukocytosis, and pain localized to the pelvis may accompany severe cuff cellulitis and most often signifies extension of the cellulitis to adjacent pelvic tissues. In such cases, broad-spectrum antibiotic therapy should be instituted with coverage for gram-negative, gram-positive, and anaerobic organisms. If purulence at the vaginal cuff is excessive or if there is a fluctuant mass noted at the vaginal cuff, the vaginal cuff should be gently probed and opened with a blunt instrument. The cuff can then be left open for dependent drainage or, alternatively, a drain can be placed into the lower pelvis through the cuff and removed when drainage, fever, and symptoms in the lower pelvic region have resolved.

Intraabdominal and Pelvic Abscess

The development of an abscess in the surgical field or elsewhere in the abdominal cavity is an uncommon complication after a gynecologic surgery. It is most likely to occur in contaminated cases in which the surgical site is not adequately drained or as a secondary complication of hematomas. **The causative pathogens in patients who have**

intra-abdominal abscesses are usually polymicrobial in nature. The aerobes most commonly identified include *E. coli*, *Klebsiella*, *Streptococcus*, *Proteus*, and *Enterobacter*. Anaerobic isolates are also common, usually from the *Bacteroides* group. These pathogens arise mainly from the vaginal tract but also can be derived from the gastrointestinal tract, particularly when the colon has been entered at the time of surgery.

Intra-abdominal abscess is sometimes difficult to diagnose. The evolving clinical picture is often one of persistent febrile episodes with a rising white blood cell count. Findings on abdominal examination may be equivocal. If an abscess is located deep in the pelvis, it may be palpable by pelvic or rectal examination. For abscesses above the pelvis, the diagnosis will depend on radiologic confirmation.

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Ultrasonography can occasionally delineate fluid collections in the upper abdomen as well as in the pelvis. However, bowel gas interference makes visualization of fluid collections or abscesses in the midabdomen difficult to distinguish. **Computed tomography scanning is, therefore, much more sensitive and specific for diagnosing intra-abdominal abscesses and often is the radiologic procedure of choice.** Occasionally, if conventional radiologic methods fail to identify an abscess and the index of suspicion for an abscess remains high, labeled leukocyte scanning may be useful for locating the infected focus.

Standard therapy for intra-abdominal abscess is evacuation and drainage combined with appropriate parenteral administration of antibiotics. Abscesses located low in the pelvis, particularly in the area of the vaginal cuff, can often be reached through a vaginal approach. In many patients, the ability to drain an abscess by placement of a drain percutaneously under CT guidance has obviated the need for surgical exploration. With CT guidance, a pigtail catheter is placed into an abscess cavity via transperineal, transrectal, or transvaginal approaches. The catheter is left in place until drainage decreases. Transperineal and transrectal drainage of deep pelvic abscesses has been successful in 90% to 93% of patients, obviating the need for surgical management (77,78). **For those patients in whom radiologic drainage is not successful, however, surgical exploration and evacuation are indicated.** The standard approach to initial antibiotic therapy has been the combination of *ampicillin*, *gentamicin*, and *clindamycin*. Adequate treatment can also be achieved with currently available broad-spectrum single agents (including the broad-spectrum *penicillin*), second- and third-generation cephalosporins, *levofloxacin* and

metronidazole, and the *sulbactam-clavulanic acid*-containing preparations (79,80,81).

Necrotizing Fasciitis

Necrotizing fasciitis is an uncommon infectious disorder; approximately 1,000 cases occur annually in the United States (82). The disorder is characterized by a rapidly progressive bacterial infection that involves the subcutaneous tissues and fascia while characteristically sparing underlying muscle. Systemic toxicity is a frequent feature of this disease, as manifested by the presence of dehydration, septic shock, disseminated intravascular coagulation, and multiple organ system failure.

The pathogenesis of necrotizing fasciitis involves a polymicrobial infection of the dermis and subcutaneous tissue. Hemolytic *streptococcus* was initially believed to be the primary pathogen responsible for the infection in necrotizing fasciitis (83). However, it is now evident that numerous other organisms are often cultured in addition to *streptococcus*, including other gram-positive organisms, coliforms, and anaerobes (83,84,85,86,87). Bacterial enzymes such as hyaluronidase and lipase released in the subcutaneous space destroy the fascia and adipose tissue and induce a liquefactive necrosis. In addition, noninflammatory intravascular coagulation or thrombosis subsequently occurs. Intravascular coagulation results in ischemia and necrosis of the subcutaneous tissues and skin (86,87). Late in the course of the infection, destruction of the superficial nerves produces anesthesia in the involved skin. The release of bacteria and bacterial toxins into the systemic circulation can cause septic shock, acid-base disturbances, and multiple organ impairment.

The diagnostic criteria for necrotizing fasciitis include extensive necrosis of the superficial fascia and subcutaneous tissue with peripheral undermining of the normal skin, a moderate to severe systemic toxic reaction, the absence of muscle involvement, *Clostridia* in wound and blood culture, major vascular occlusion, intensive leukocytic infiltration, and necrosis of subcutaneous tissue (88).

Most patients with necrotizing fasciitis suffer pain, which in the early stages of the disease is often disproportionately greater than that expected from the degree of

cellulitis present. Late in the course of the infection, the involved skin may actually be anesthetized secondary to necrosis of superficial nerves. Temperature abnormalities, both hyperthermia and hypothermia, are common concomitant with the release of bacterial toxins as well as with bacterial sepsis, which is present in up to 40% of patients (89). The involved skin is initially tender, erythematous, and warm. Edema develops, and the erythema spreads diffusely, fading into normal skin, characteristically without distinct margins or induration. Subcutaneous microvascular thrombosis induces ischemia in the skin, which becomes cyanotic and blistered. Eventually, as necrosis develops, the skin becomes gangrenous and may slough spontaneously. Most patients will have leukocytosis and acid-base abnormalities. Finally, subcutaneous gas may develop, which can be identified by palpation and by radiography. The finding of subcutaneous gas by radiography is often indicative of clostridial infection, although it is not a specific finding and may be caused by other organisms. These organisms include *Enterobacter*, *Pseudomonas*, anaerobic streptococci, and *Bacteroides*, which, unlike clostridial infections, spare the muscles underlying the affected area (90). A tissue biopsy specimen for Gram stain and aerobic and anaerobic culture should be obtained from the necrotic center of the lesion to identify the etiologic organisms (87). Although necrotizing fasciitis often is diagnosed during surgery, a high index of suspicion as well as liberal use of frozen-section biopsy can often provide an early life-saving diagnosis and minimize morbidity (91).

Predisposing risk factors for necrotizing fasciitis include diabetes mellitus, alcoholism, an immunocompromised state, hypertension, peripheral vascular disease, intravenous drug abuse, and obesity (82,85,86,90,92). The most frequent site of infection has been in the extremities (87), but the infection can occur anywhere in the subcutaneous tissues, including the head and neck, trunk, and perineum. Necrotizing fasciitis has been known to occur after trauma, surgery, burns, and lacerations; as a secondary complication in perirectal infections or Bartholin duct abscesses; and *de novo* (82,83,86,87,91). Increased age, delay in diagnosis, inadequate debridement during initial surgery, extensive disease at the time of diagnosis, and the presence of diabetes mellitus are all factors that have been associated with an increased likelihood of mortality from necrotizing fasciitis (82,89). Early diagnosis and aggressive management of this lethal disease have led to improved survival. In an earlier series, the mortality rate was consistently higher than 30%; in more recent series, the mortality rate has decreased to less than 10% (90,93,94).

Successful management of necrotizing fasciitis involves early recognition,

immediate initiation of resuscitative measures (including correction of fluid, acid-base, electrolyte, and hematologic abnormalities), aggressive surgical debridement and redebridement as necessary, and broad-spectrum antibiotic therapy. Many patients will benefit from central venous monitoring, as well as from high-caloric nutritional support.

During surgery, the incision should be made through the infected tissue down to the fascia. An ability to undermine the skin and subcutaneous tissues with digital palpation often will confirm the diagnosis. Multiple incisions can be made sequentially toward the periphery of the affected tissue until well-vascularized, healthy, resistant tissue is reached at all margins. The remaining affected tissue must be excised. The wound can then be packed and sequentially debrided on a daily basis as necessary until healthy tissue is displayed at all margins. **Hyperbaric oxygen therapy may be of some benefit, particularly in patients for whom culture results are positive for anaerobic organisms.** Retrospective nonrandomized studies have demonstrated that the addition of hyperbaric oxygen therapy to surgical debridement and antimicrobial therapy appear to significantly decrease both wound morbidity and overall mortality in patients with necrotizing fasciitis (82,95). The benefit of hyperbaric therapy shown in one study was remarkable, given that patients

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receiving hyperbaric oxygen were sicker and had a higher incidence of diabetes mellitus, leukocytosis, and shock (82).

After the initial resuscitative efforts and surgical debridement, the primary concern is the management of the open wound. Allograft and xenograft skin can be used to cover open wounds, thus decreasing heat and evaporative water loss. Interestingly, temporary biologic closure of open wounds also seems to decrease bacterial growth (96). Amniotic membranes have also been shown to be an effective wound covering in patients with necrotizing fasciitis (92). A new technology that has been demonstrated in laboratory and clinical studies to significantly improve wound healing is a vacuum-assisted closure (VAC) method that uses a subatmospheric pressure technique (97,98). In situations in which spontaneous closure is not likely, the VAC device may allow for the development of a suitable granulation bed and prepare the tissue for graft placement, thereby increasing the probability of graft survival. Finally, skin flaps can be mobilized to help cover open wounds once the infections have resolved and granulation has begun.

Gastrointestinal Preparation

Preparation of the lower gastrointestinal tract before elective gynecologic surgery has several goals. In most gynecologic surgery, when the gastrointestinal tract is not entered, mechanical preparation of the bowel reduces gastrointestinal contents and thus allows more room in the abdomen and pelvis, facilitating the surgical procedure. If a rectosigmoid colon enterotomy occurs, the mechanical bowel preparation eliminates formed stool and reduces the risk of bacterial contamination, thus reducing infectious complications. Mechanical bowel preparation may be accomplished as presented in (Table 20.9). The traditional use of laxatives and enemas requires at least 12 to 24 hours and generally causes moderate abdominal distention and crampy pain. Randomized trials comparing traditional mechanical bowel preparation with oral gut lavage (*PEG electrolyte solution, GoLYTELY*) have found that the use of approximately 4 L of *GoLYTELY* (administered until the rectal effluent is clear) provides more complete, faster, and more comfortable bowel preparation (99). However, the ingestion of 4 L of fluid is problematic for many patients. **An alternative mechanical preparation method is the use of oral sodium phosphate (*Phospho-Soda*). When evaluated in a randomized trial comparing the 4 L of *GoLYTELY* with oral sodium phosphate, colonoscopic examination disclosed that both methods were equally effective in colonic cleansing, and more patients preferred the sodium phosphate method (100).**

Table 20.9 Intestinal Preparation

Preoperative Day 2 Clear liquid diet

Preoperative Day 1 Clear liquid diet

Mechanical Prep

Fleet Phospho-Soda Saline Laxative (3 oz. bottle)
(one bottle of laxative 1 p.m. and another at 7 p.m.)
Fleet enemas until no solid stool in p.m. (Optional)

Antibiotic Prep (Optional)

Neomycin (oral), 1 g q 4 h for three doses (4, 8, 12 p.m.)
Erythromycin (oral), 1 g q 4 h for three doses

Day of Surgery Fleet enemas until clear (Optional)

High infection rates after colonic surgery have led to investigation of methods aimed at reducing these significant complications. Although mechanical bowel preparation is an essential part of all colonic surgery preparation regimens, it does not reduce the infection rate satisfactorily. Reduction of the number of pathogenic flora in the colon is the primary strategy to reduce infection after colonic surgery. The colon has the greatest concentration of bacteria in the body, including both aerobes and anaerobes. Anaerobes outnumber aerobes by 1,000:1. After reducing the bacterial load by mechanical preparation, the administration of antibiotics can further reduce the bacterial count in the colon. Of the many trials reported, the most widely accepted regimen combines *erythromycin* base and *neomycin* administered orally (see Table 20.9) (101,102,103). Many surgeons substitute *metronidazole* for the *erythromycin*; there is no significant difference in infection rates, but patients tolerate *metronidazole* better than *erythromycin*. **The use of oral antibiotics 24 hours before colonic resection has reduced the infection rate from approximately 40% to 5% to 10% in randomized trials.** Because these oral antibiotics are poorly absorbed and many do little to reduce infection from vaginal contamination, an intravenous antibiotic (first-generation cephalosporin) can be added to the preoperative regimen. **Antibiotic bowel prophylaxis should be used for patients who are likely to undergo colorectal surgery (pelvic exenteration, ovarian cancer debulking) and those who are at high risk for rectal injury (such as severe cases of endometriosis or pelvic inflammatory disease).**

Postoperative Gastrointestinal Complications

Ileus

Following abdominal or pelvic surgery, most patients will experience some degree of intestinal ileus. The exact mechanism by which this arrest and disorganization of gastrointestinal motility occurs is unknown, but it appears to be associated with the opening of the peritoneal cavity and is aggravated by manipulation of the intestinal tract and prolonged surgical procedures. Infection, peritonitis, and electrolyte disturbances may also result in ileus. For most patients undergoing common gynecologic operations, the degree of ileus

is minimal, and gastrointestinal function returns relatively rapidly, allowing the resumption of oral intake within a few days of surgery. Patients who have persistently diminished bowel sounds, abdominal distention, and nausea and vomiting require further evaluation and more aggressive management.

Ileus is usually manifested by abdominal distention and should be evaluated initially by physical examination. Pertinent points of the abdominal examination include assessment of the quality of bowel sounds and palpation in search of tenderness or rebound. The possibility that the patient's signs and symptoms may be associated with a more serious intestinal obstruction or other intestinal complication must be considered. Pelvic examination should be performed to evaluate the possibility of a pelvic abscess or hematoma that may contribute to the ileus. **Abdominal radiography to evaluate the abdomen in the flat (supine) position as well as in the upright position usually will aid in the diagnosis of an ileus. The most common radiographic findings include dilated loops of small and large bowel as well as air-fluid levels while the patient is in the upright position.** Sometimes, massive dilation of the colon or stomach may be noted. The remote possibility of distal colonic obstruction suggested by a dilated cecum should be excluded by rectal examination, proctosigmoidoscopy, or barium enema. In the postoperative gynecology patient, especially in the upright position, the flat plate of the abdomen may also show evidence of free air. This common finding following surgery lasts 7 to 10 days in some instances and is not indicative of a perforated viscus in most patients.

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The initial management of a postoperative ileus is aimed at gastrointestinal tract decompression and maintenance of appropriate intravenous replacement fluids and electrolytes.

- **A nasogastric tube should be used to evacuate the stomach of its fluid and gaseous contents.** Prolonged nasogastric suction continues to remove swallowed air, which is the most common source of air in the small bowel. Some clinicians prefer to use a longer small intestinal tube (Cantor or Miller-Abbott tube) (103). This tube, which usually has a mercury-filled bag on its distal tip, may be propelled by peristalsis through the pylorus and into the small bowel, thus allowing better evacuation of the small bowel. The disadvantage of long tubes is that they take a longer time to become positioned and may not enter the small bowel as

a result of the decreased intestinal motility associated with ileus.

- **Fluid and electrolyte replacement must be adequate to keep the patient well perfused.** Significant amounts of third-space fluid loss occur in the bowel wall, the bowel lumen, and the peritoneal cavity during the acute episode. Gastrointestinal fluid losses from the stomach may lead to a metabolic alkalosis and depletion of other electrolytes as well. Careful monitoring of serum chemistry levels and appropriate replacement are necessary.
- **Most cases of severe ileus will begin to improve over a period of several days.** In general, this improvement is recognized by reduction in the abdominal distention, return of normal bowel sounds, and passage of flatus or stool. Follow-up abdominal radiographs should be obtained as necessary for further monitoring.
- **When the gastrointestinal tract function appears to have returned to normal, the nasogastric tube may be removed and a liquid diet may be instituted.**
- **If a patient shows no evidence of improvement during the first 48 to 72 hours of medical management, other causes of ileus should be sought.** Such cases may include ureteral injury, peritonitis from pelvic infection, unrecognized gastrointestinal tract injury with peritoneal spill, or fluid and electrolyte abnormalities such as hypokalemia. With persistent ileus, the use of water-soluble upper gastrointestinal contrast studies may assist in the resolution, but prospective randomized data regarding this maneuver are lacking.

Small Bowel Obstruction

Obstruction of the small bowel following major gynecologic surgery occurs in approximately 1% to 2% of patients (104). The most common cause of small bowel obstruction is adhesions to the operative site. If the small bowel becomes adherent in a twisted position, partial or complete obstruction may result from distention, ileus, or bowel wall edema. Less common causes of postoperative small bowel obstruction include entrapment of the small bowel into an incisional hernia and an unrecognized defect in the small bowel or

large bowel mesentery. **Early in its clinical course, a postoperative small bowel obstruction may exhibit signs and symptoms identical to those of ileus. Initial conservative management as outlined for the treatment of ileus is appropriate.** Because of the potential for mesenteric vascular occlusion and resulting ischemia or perforation, worsening symptoms of abdominal pain, progressive distention, fever, leukocytosis, or acidosis should be evaluated carefully because immediate surgery may be required.

In most cases of small bowel obstruction following gynecologic surgery, the obstruction is only partial and the symptoms usually resolve with conservative management.

- **Further evaluation after several days of conservative management may be necessary.** Evaluation of the gastrointestinal tract with barium enema and an

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upper gastrointestinal study with small bowel assessment are appropriate. In most cases, complete obstruction is not documented, although a narrowing or tethering of the segment of small bowel may indicate the site of the problem.

- **Further conservative management with nasogastric decompression and intravenous fluid replacement may allow time for bowel wall edema or torsion of the mesentery to resolve.**

- **If resolution is prolonged and the patient's nutritional status is marginal, the use of TPN may be necessary.**

- **Conservative medical management of postoperative small bowel obstruction usually results in complete resolution.** However, if persistent evidence of small bowel obstruction remains after full evaluation and an adequate trial of medical management, exploratory laparotomy may be necessary to evaluate surgically and manage the obstruction. In most cases, lysis of adhesions is all that is required, although a segment of small bowel that is badly damaged or extensively sclerosed from adhesions may require

resection and reanastomosis.

Colonic Obstruction

Postoperative colonic obstruction following surgery for most gynecologic conditions is exceedingly rare. It is almost always associated with a pelvic malignancy, which in most cases will have been known at the time of the initial operation. Advanced ovarian carcinoma is the most common cause of colonic obstruction in postoperative gynecologic surgery patients, and it is caused by extrinsic impingement on the colon by the pelvic malignancy. Intrinsic colonic lesions may be undetected, especially in a patient with some other benign gynecologic condition. When colonic obstruction is manifested by abdominal distention and abdominal radiography reveals a dilated colon and enlarging cecum, further evaluation of the large bowel is required by barium enema or colonoscopy. **Dilation of the cecum to more than 10 to 12 cm in diameter as viewed by abdominal radiography requires immediate evaluation and surgical decompression by performing colectomy or colostomy.** Surgery should be performed as soon as the obstruction is documented. Conservative management of colonic obstruction is not appropriate because the complication of colonic perforation has an exceedingly high mortality rate.

Diarrhea

Episodes of diarrhea often occur following abdominal and pelvic surgery as the gastrointestinal tract returns to its normal function and motility. However, prolonged and multiple episodes may represent a pathologic process such as impending small bowel obstruction, colonic obstruction, or pseudomembranous colitis. Excessive amounts of diarrhea should be evaluated by abdominal radiography and stool samples tested for the presence of ova and parasites, bacterial culture, and *Clostridium difficile* toxin. Proctoscopy and colonoscopy may also be advisable in severe cases. Evidence of intestinal obstruction should be managed as outlined previously. Infectious causes of diarrhea should be managed with the appropriate antibiotics as well as fluid and electrolyte replacement. ***C. difficile*-associated pseudomembranous colitis may result from exposure to any antibiotic. Discontinuation of these antibiotics (unless they are needed to treat another severe infection) is advisable, along with the institution of appropriate**

therapy. Oral *metronidazole* is a suitable agent for instituting therapy and is less expensive than *vancomycin*. Therapy should be continued until the diarrhea abates, and several weeks of oral therapy may be required to obtain complete resolution of the pseudomembranous colitis.

Fistula

Gastrointestinal fistulas are relatively rare following gynecologic surgery. They are most often associated with malignancy, prior radiation therapy, or surgical injury to the large or

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small bowel that was improperly repaired or unrecognized. Signs and symptoms of gastrointestinal fistula are often similar to those of small bowel obstruction or ileus, except that a fever is usually a more prominent component of the patient's symptoms. When fever is associated with gastrointestinal dysfunction postoperatively, evaluation should include early assessment of the gastrointestinal tract to confirm its continuity. **When fistula is suspected, the use of water-soluble gastrointestinal contrast material is advised to avoid the complication of barium peritonitis.** Evaluation with abdominal pelvic CT scan may also assist in identification of a fistula and associated abscess. **Recognition of an intraperitoneal gastrointestinal leak or fistula formation usually requires immediate surgery, unless the fistula has drained spontaneously through the abdominal wall or vaginal cuff.**

An enterocutaneous fistula arising from the small bowel and draining spontaneously through the abdominal incision may be managed successfully with medical therapy. Therapy should include nasogastric decompression, replacement of intravenous fluids as well as TPN, and appropriate antibiotics to treat an associated mixed bacterial infection. If the infection is under control and there are no other signs of peritonitis, the surgeon may consider allowing potential resolution of the fistula over a period of up to 2 weeks. Some authors have suggested the use of *somatostatin* to decrease intestinal tract secretion and allow earlier healing of the fistula. In some cases, the fistula will close spontaneously with this mode of management. If the enterocutaneous fistula does not close with conservative medical management, surgical correction with resection, bypass, or reanastomosis will be necessary.

A *rectovaginal fistula* that occurs following gynecologic surgery is usually the result of

surgical trauma that may have been aggravated by the presence of extensive adhesions in the rectovaginal septum associated with endometriosis, pelvic inflammatory disease, or pelvic malignancy. **A small rectovaginal fistula may be managed with a conservative medical approach, in the hope that decreasing the fecal stream will allow closure of the fistula.** A small fistula that allows continence except for an occasional leak of flatus may be managed conservatively until the inflammatory process in the pelvis resolves. At that point, usually several months later, correction of the fistula is appropriate. Large rectovaginal fistulas for which there is no hope of spontaneous closure are best managed by performing an initial diverting colostomy followed by repair of the fistula after inflammation has resolved. After the fistula closure is healed and deemed successful, the colostomy can be closed.

Thromboembolism

Risk Factors

Deep venous thrombosis and pulmonary embolism are largely preventable, yet remain a significant complication in postoperative patients. The magnitude of this problem is relevant to the gynecologist, because **40% of all deaths following gynecologic surgery are directly attributed to pulmonary emboli** (105), and it is the most frequent cause of postoperative death in patients with uterine or cervical carcinoma (106).

The causal factors of venous thrombosis were first proposed by Virchow in 1858 and include a hypercoagulable state, venous stasis, and vessel endothelial injury. Risk factors include major surgery; advanced age; nonwhite race; malignancy; history of deep venous thrombosis, lower extremity edema, or venous stasis changes; presence of varicose veins; being overweight; a history of radiation therapy; and hypercoagulable states, such as factor V Lieden, pregnancy, use of oral contraceptives, estrogens, or *tamoxifen*. Intraoperative factors associated with postoperative deep venous thrombosis included increased anesthesia time, increased blood loss, and the need for transfusion in the operating room. It is important to recognize these risk factors to provide the appropriate level

of venous thrombosis prophylaxis (107,108). A general outline of levels of thromboembolism risk are listed in Table 20.10.

Table 20.10 Thromboembolism Risk Stratification*Low Risk*

Minor surgery

No other risk factors^a*Moderate Risk*

Age >40 years and major surgery

Age <40 years with other risk factors^a and major surgery*High Risk*

Age >60 years and major surgery

Cancer

History of deep venous thrombosis or pulmonary embolism

Thrombophilias

Highest Risk

Age >60 and cancer or history of venous thromboembolism

^aRisk factors: obesity, varicose veins, history of deep venous thrombosis or pulmonary embolism, current estrogen, *tamoxifen*, or oral contraceptive use.

Prophylactic Methods

A number of prophylactic methods have been shown to significantly reduce the incidence of deep venous thrombosis, and a few studies have included a large enough patient population to show a reduction in fatal pulmonary emboli. The ideal prophylactic method would be effective, free of significant side effects, well accepted by the patient and nursing staff, widely applicable to most patients, and inexpensive.

Low-Dose Heparin

The use of small doses of subcutaneously administered *heparin* for the prevention of deep venous thrombosis and pulmonary embolism is the most widely studied of all prophylactic methods. **More than 25 controlled trials have demonstrated that *heparin* given subcutaneously 2 hours preoperatively and every 8 to 12 hours postoperatively**

is effective in reducing the incidence of deep venous thrombosis. The value of low-dose *heparin* in preventing fatal pulmonary emboli was established by a randomized, controlled, multicenter international trial, which demonstrated a significant reduction in fatal postoperative pulmonary emboli in general surgery patients receiving low-dose *heparin* every 8 hours postoperatively (109). Trials of low-dose *heparin* in gynecologic surgery patients have shown a significant reduction in postoperative deep venous thrombosis.

Although low-dose *heparin* is considered to have no measurable effect on coagulation, most large series have noted an increase in the bleeding complication rate, especially a higher incidence of wound hematoma (110). Although relatively rare, thrombocytopenia is associated with low-dose *heparin* use and has been found in 6% of patients after gynecologic surgery (110). If patients remain on low-dose *heparin* for more than 4 days, it is reasonable to check their platelet count to assess the possibility of *heparin*-induced thrombocytopenia.

Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWH) are fragments of *heparin* that vary in size from 4,500 to 6,500 daltons. When compared with unfractionated *heparin*, *LMWH* have more anti-Xa and less antithrombin activity, leading to less effect on partial thromboplastin time and possibly also leading to fewer bleeding complications (111). An increased half-life of 4 hours results in increased bioavailability when compared with unfractionated *heparin*. The increase in half-life of *LMWH* also allows the convenience of once-a-day dosing.

Randomized controlled trials have compared *LMWH* with unfractionated *heparin* in patients undergoing gynecologic surgery. In all studies, there was a similar incidence of deep venous thrombosis (DVT). Bleeding complications were also similar between the unfractionated *heparin* and *LMWH* groups (112). A meta-analysis of general surgery and gynecological surgery patients from 32 trials likewise indicated that daily *LMWH* administration is as effective as unfractionated *heparin* in DVT prophylaxis without any difference in hemorrhagic complications (113).

Mechanical Methods

Stasis in the veins of the legs occurs while the patient is undergoing surgery and continues postoperatively for varying lengths of time. Stasis occurring in the capacitance veins of the calf during surgery, plus the hypercoagulable state induced by surgery, are the prime factors contributing to the development of acute postoperative DVT. Prospective studies of the natural history of postoperative DVT have shown that the calf veins are the predominant site of thrombi and that most thrombi develop within 24 hours of surgery (114).

Although probably of only modest benefit, reduction of stasis by short preoperative hospital stays and early postoperative ambulation should be encouraged for all patients. Elevation of the foot of the bed, raising the calf above heart level, allows gravity to drain the calf veins and should further reduce stasis.

Elastic Stocking

Controlled studies of graduated pressure stockings are limited but do suggest modest benefit when they are carefully fitted (115). Poorly fitted stockings may be hazardous to some patients who develop a tourniquet effect at the knee or mid thigh (106). Variations in human anatomy do not allow perfect fit of all patients to available stocking sizes. The simplicity of elastic stockings and the absence of significant side effects are probably the two most important reasons that they are often included in routine postoperative care.

External Pneumatic Compression

The largest body of literature dealing with the reduction of postoperative venous stasis deals with intermittent external compression of the leg by pneumatically inflated sleeves placed around the calf or leg during intraoperative and postoperative periods. Various pneumatic compression devices and leg sleeve designs are available, and the current literature has not demonstrated superiority of one system over another. **Calf compression during and after gynecologic surgery significantly reduces the incidence of DVT on a level similar to that of low-dose *heparin*.** In addition to increasing venous flow and pulsatile emptying of the calf veins, external pneumatic compression also appears to augment endogenous fibrinolysis, which may result in lysis of very early thrombi before they become clinically significant (116).

The duration of postoperative external pneumatic compression has differed in various trials. External pneumatic compression may be effective when used in the operating room and for the first 24 hours postoperatively in patients with benign conditions who will ambulate on the first postoperative day (116,117).

External pneumatic compression used in patients undergoing major surgery for gynecologic malignancy has been found to reduce the incidence of postoperative venous thromboembolic complications by nearly threefold (118), but only if calf compression was applied intraoperatively and for the first 5 postoperative days (119). Patients with gynecologic malignancies may remain at risk for a longer period than general surgical patients because of stasis and hypercoagulable states; therefore, these patients appear to benefit from longer use of external pneumatic compression.

External pneumatic leg compression has no significant side effects or risks and is considered slightly more cost-effective when compared with pharmacologic methods of prophylaxis (120). Of course, compliance in wearing the leg compression while in bed is of utmost importance, and the patient and nursing staff should be educated to the proper regimen for maximum benefit.

Management of Postoperative Deep Venous Thrombosis and Pulmonary Embolism

Because pulmonary embolism is the leading cause of deaths following gynecologic surgical procedures, identification of high-risk patients and the use of prophylactic venous thromboembolism regimens is an essential part of management (105,106,121). In addition, the early recognition of DVT and pulmonary embolism and immediate treatment are critical. Most pulmonary emboli arise from the deep venous system of the leg following gynecologic surgery; the pelvic veins are a known source of fatal pulmonary emboli as well.

The signs and symptoms of DVT of the lower extremities include pain, edema, erythema, and prominent vascular pattern of the superficial veins. These signs and symptoms are relatively nonspecific; 50% to 80% of patients with these symptoms will not actually have

DVT (122). Conversely, approximately 80% of patients with symptomatic pulmonary emboli have no signs or symptoms of thrombosis in the lower extremities (123). Because of the lack of specificity when signs and symptoms are recognized, additional tests should be performed to establish the diagnosis of DVT.

Diagnosis

Doppler Ultrasound

B-mode duplex Doppler imaging is currently the most common technique for the diagnosis of symptomatic venous thrombosis, especially when it arises in the proximal lower extremity. With duplex Doppler imaging, the femoral vein can be visualized and clots may be seen directly (124). Compression of the vein with the ultrasound probe tip allows assessment of venous collapsibility; the presence of a thrombus diminishes vein wall collapsibility. It should be recognized that Doppler imaging is less accurate when evaluating the calf and the pelvic veins.

Venography

Although venography has been the standard technique for diagnosis of DVT, other diagnostic studies are accurate when performed by a skilled technologist and, in most patients, may replace the need for routine contrast venography. Venography is moderately uncomfortable, requires the injection of a contrast material that may cause allergic reaction or renal injury, and may result in phlebitis in approximately 5% of patients (125). However, if the results of noninvasive imaging are normal or inconclusive and the clinician remains concerned given clinical symptoms, venography should be performed to obtain a definitive answer.

Magnetic Resonance Venography (MRV)

In addition to having a sensitivity and specificity comparable to venography, MRV may detect thrombi in pelvic veins that are not imaged by venography (126). The primary drawback to MRV is the time involved in examining the lower extremity and pelvis as well as the expense of this technology.

Treatment

Deep Venous Thrombosis

The treatment of postoperative DVT requires the immediate institution of anticoagulant therapy. Treatment may be with either *unfractionated heparin* or *LMWH*, followed by 6 months of oral anticoagulant therapy with *warfarin (Coumadin)*.

Unfractionated Heparin

After venous thromboembolism is diagnosed, *unfractionated heparin* should be initiated to prevent proximal propagation of the thrombus and allow physiological thrombolytic pathways to dissolve the clot. An initial bolus of 80 units per kilogram is given intravenously, followed by a continuous infusion of 1,000 to 2,000 units per hour (18 units/kg/hour). ***Heparin dosage is adjusted to maintain activated partial thromboplastin time (APTT) levels at a therapeutic level 1.5 to 2.5 times the control value.*** Initial APTT should be measured after 6 hours of *heparin* administration and the dose adjusted as necessary. Patients having subtherapeutic APTT levels in the first 24 hours have a risk of recurrent thromboembolism 15 times the risk of patients with appropriate levels. Patients, therefore, should be managed aggressively using intravenous *heparin* to achieve prompt anticoagulation. A weight-based nomogram is helpful in achieving a therapeutic APTT level (Table 20.11) (127). ***Oral anticoagulant (warfarin) administration should be started on the first day of heparin infusion. The international normalized ration (INR) should be monitored daily until a therapeutic level is achieved (2.0–3.0).*** The change in the INR resulting from *warfarin* administration often precedes the anticoagulant effect by approximately 2 days, during which time low protein C levels are associated with a transient hypercoagulable state. Therefore, *heparin* should be administered until the INR has been maintained in a therapeutic range for at least 2 days, confirming proper *warfarin* dose. Intravenous *heparin* may be discontinued in 5 days if an adequate IRN level has been established.

Table 20.11 Heparin Administration for Treatment of Deep Venous Thrombosis or Pulmonary Embolism: Weight-Based Nomogram

<i>Time of Administration</i>	<i>Dose</i>
Initial dose	80-U/kg bolus, then 18 U/kg/h
The APTT^a should be measured every 6 h and the heparin dose adjusted as follows:	
APTT <35 seconds (<1.2 × control)	80-U/kg bolus, then 4 U/kg/h
APTT 35–45 seconds (1.2–1.5 × control)	40-U/kg bolus, then 2 U/kg/h
APTT 46–70 seconds (1.5–2.3 × control)	No change
APTT 71–90 seconds (2.3–3 × control)	Decrease infusion rate by 2 U/kg/h
APTT >90 seconds (>3 × control)	Hold infusion for 1 h, then decrease infusion rate by 3 U/kg/h

^aAPTT, activated partial thromboplastin time.

Reprinted from **Raschke RA, Reilly BM, Guidry JR, et al.** The weight-based heparin dosing nomogram compared with a "standard care" nomogram. *Ann Intern Med* 1993;119:874–881, with permission.

Low-Molecular-Weight Heparin

Two LMWH preparations (*exoxaparin* and *daltaparin*) have been shown to be effective in the treatment of venous thromboembolism and have a cost-effective advantage over intravenous *heparin* in that they may be administered in the outpatient setting.

The dosages used in treatment of thromboembolism are unique and weight-adjusted according to each LMWH preparation. Because LMWH have a minimal effect on APPT, serial laboratory monitoring of these levels is not necessary. Similarly, monitoring of anti-Xa activity (except in difficult cases or those with renal impairment) has not been shown to be of significant benefit in a dose adjustment of

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LMWH. The increased bioavailability associated with LMWH allows for twice-a-day dosing, potentially making outpatient management for a subset of patients an option. **A meta-analysis involving more than 4,000 patients from 22 trials suggests that LMWH is more effective, safer, and less costly when compared with unfractionated heparin in preventing recurrent thromboembolism (128).**

Pulmonary Embolism

Many of the signs and symptoms of pulmonary embolism are associated with other, more commonly occurring pulmonary complications following surgery. **The classic findings of pleuritic chest pain, hemoptysis, shortness of breath, tachycardia, and tachypnea should alert the physician to the possibility of a pulmonary embolism.** Many times, however, the signs are much more subtle and may be suggested only by a persistent tachycardia or a slight elevation in the respiratory rate. Patients suspected of pulmonary embolism should be evaluated initially by chest x-ray, electrocardiography, and arterial blood gas assessment. Any evidence of abnormality should be further evaluated by ventilation-perfusion lung scan, or a spiral CT scan of the chest. Unfortunately, a high percentage of lung scans may be interpreted as "indeterminate." In this setting, careful clinical evaluation and judgment are required to decide whether pulmonary arteriography should be performed to document or exclude the presence of a pulmonary embolism.

The treatment of pulmonary embolism is as follows:

- Immediate anticoagulant therapy, identical to that outlined for the treatment of DVT, should be initiated.
- Respiratory support, including oxygen and bronchodilators and an intensive care setting, may be necessary.
- Although massive pulmonary emboli are usually quickly fatal, pulmonary embolectomy has been performed successfully on rare occasions.
- Pulmonary artery catheterization with the administration of thrombolytic agents bears further evaluation and may be important in patients with massive pulmonary embolism.
- Vena cava interruption may be necessary in situations in which anticoagulant therapy is

ineffective in the prevention of rethrombosis and repeated embolization from the lower extremities or pelvis. A vena cava umbrella or filter may be inserted percutaneously above the level of the thrombosis and caudad to the renal veins. In most cases, however, anticoagulant therapy is sufficient to prevent repeat thrombosis and embolism and to allow the patient's own endogenous thrombolytic mechanisms to lyse the pulmonary embolus.

Management of Medical Problems

Endocrine Disease

The three most frequent endocrine disorders that occur in patients undergoing gynecologic surgery are diabetes mellitus, thyroid disease, and adrenal abnormalities. The pathophysiology of these disorders aids in understanding the effects of surgery on patients with these problems.

Diabetes Mellitus

According to the American Diabetes Association, 9.3 million American women, or 8.7% of all women older than 20 years, suffer from diabetes (129). Approximately 50% of

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individuals with diabetes mellitus (DM) will have surgery during their life (130). Many of these procedures are a direct result of the complications of DM: retinopathy, nephropathy, large- and small-vessel occlusive disease, and coronary artery disease. It is the direct effect of DM on the end organs that determines the risk of surgery rather than the type or duration or the control of the condition itself. Diabetes mellitus is a complicated medical disorder of glucose metabolism that is related to a lack of production of or resistance to *insulin*.

Patients with DM experience exaggerated hyperglycemia during surgery. This hyperglycemia is multifactorial in origin and is secondary to increased catecholamine production, which inhibits pancreatic release of insulin and causes increased insulin resistance at the end organs. Elevations in instrumental hormones, such as cortisol, growth hormone, and glucagon, also enhance gluconeogenesis and glycogenolysis (131). Goals of the preoperative assessment and perioperative management are to ensure metabolic homeostasis

and to anticipate problems arising from pre-existing complications.

Preoperative Risk Assessment

Preoperative risk assessment for diabetes should begin with a review of systems. Nocturia, polyuria, polydipsia, glucosuria, obesity, previous gestational diabetes, ethnicity, and family history are relevant aspects of the history. The current recommendations for establishing a diagnosis of diabetes are as follows (132):

- Polyuria, polydipsia, unexplained weight loss with a random nonfasting glucose of >200 mg/dL, *or*
- Fasting glucose >126 mg/dL, *or*
- Two-hour postprandial 75 g glucose drink with serum glucose >200 mg/dL

Confirmation of the diagnosis requires a second test on a different day.

Preoperative risk assessment in the previously diagnosed individual with diabetes should begin with the knowledge of the patient's routine glucose management strategies, medications, and baseline hemoglobin A_{1c} (133). The presence of end-organ complications of diabetes should also be documented.

Large- and small-vessel arterial occlusive disease is the single most important risk factor in the preoperative setting.

A careful history and physical examination should be performed to determine the presence or absence of coronary artery or cerebral vascular disease (130). When extended surgery is possible, as with surgery for gynecologic cancer, exercise stress testing or dipyridamole-thallium imaging should be considered to rule out occult coronary artery disease. Preoperative and intraoperative administration of beta-blockers should be considered for patients undergoing surgery (134). Assessment of end-organ disease in the retina, kidney, and carotid arteries or evidence of peripheral vascular disease by the presence of foot ulcers should alert the clinician to the presence of small-or

Imaging studies using contrast dye should be avoided and alternative testing should be performed to reduce the incidence of acute tubular necrosis. If a contrast study must be performed, adequate hydration both before and after the procedure is essential, and oral metformin should be withheld for 24 to 48 hours after the procedure.

Preoperative evaluation should include examination of the skin and urine sediment to detect asymptomatic infection. Wound infections, skin infections, pneumonia, and urinary tract infections account for two thirds of the postoperative complications in patients with diabetes (131). There is a known predisposition for patients with DM to have gram-negative and staphylococcal pneumonia as well as an increased incidence of gram-negative and

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group B streptococcal sepsis (135). Seven percent of individuals with diabetes will have postoperative gram-negative sepsis, a rate approximately seven times higher than of the nondiabetic population. These complications occur more often in patients with poor glucose control, probably caused by impaired leukocyte function in the presence of hyperglycemia (136,137). Individuals with DM have an increased risk of wound dehiscence and wound infection, as well as decreased amounts of collagen formation, fibroblast growth, and capillary growth, presumably secondary to the pathophysiology of small-vessel disease (138,139,140). Autonomic neuropathy has been documented in patients with DM, and these autonomic impairments can lead to intraoperative hypotension, cardiac arrhythmias, and sudden death as well as abnormal motility of the esophagus, stomach, and small intestine (131). Peripheral sensory and motor neuropathies may or may not be present. The presence of any manifestations of autonomic neuropathy intraoperatively should prompt close monitoring of the affected organ system in the postoperative period.

The traditional goal for glucose control during surgery is to maintain the glucose level between 150 mg/dL and 200 mg/dL. Perioperative hyperglycemia (greater than 250 mg/dL) is associated with increased susceptibility to infection and poor wound healing. Extreme hyperglycemia predisposes type I DM patients to metabolic acidosis, and surgery should be canceled until normal acid-base balance has been documented. Hyperosmolar hyperglycemic nonketotic states must be recognized before surgery. Electrolyte disturbances, especially those related to sodium and potassium, should be corrected preoperatively. Hypoglycemia should be avoided during the perioperative period.

The history and type of DM are important factors to consider when devising a perioperative management plan. Patients with noninsulin-dependent diabetes (type II) whose condition is controlled with oral hypoglycemic agents or diet are best treated with intravenous fluids containing no dextrose and generally should not be given insulin intraoperatively. Oral administration of hypoglycemic agents should be discontinued approximately 24 hours before the surgery, and hyperglycemic episodes in the perioperative period are treated with sliding-scale regular *insulin* only for blood sugar levels in excess of 250 mg/dL.

Insulin-dependent or type I diabetes poses a more difficult problem. Preoperatively, the goals include avoiding ketoacidosis and hypoglycemia, as well as, to a lesser extent, hyperglycemia. Traditionally, approximately one third to one half of the patient's usual daily dose of NPH insulin (intermediate acting) is given subcutaneously the morning of surgery. An infusion of 5% dextrose is then given intraoperatively and additional regular insulin can be administered in the operating room. Alternatively, a continuous infusion of insulin and glucose in a fixed ratio has been advocated (130).

The patient is much more prone to significant hypoglycemia, however, when a continuous infusion of insulin is given. Because of the severe implications associated with intraoperative hypoglycemia, this method may pose additional risks. There is no single regimen that is clearly superior for the intraoperative management of type I diabetic patients. However, a continuous intravenous *insulin* infusion is indicated for patients with unstable type I diabetes, those who require emergency surgery while in ketoacidosis, and those undergoing long, complex procedures (136). Consultation with endocrine and anesthesia colleagues can be helpful in managing these complex regimens.

Postoperative Management

Postoperative monitoring of patients with DM includes careful monitoring of serum glucose levels.

If an intravenous insulin regimen has been used, blood glucose levels must be checked every 1 to 2 hours. If a sliding-scale insulin administration is to be used, blood glucose should be checked and documented approximately every 6 hours until the patient is eating and stable on her preoperative regimen. The serum glucose level should be maintained at less than 250 mg/dL, and ideally in the "inpatient glycemic 'hot spot'" between 100 and 200 mg/dL (130).

It is essential to prevent the development of severe hypoglycemia or hyperglycemia and the associated complications of diabetic ketoacidosis or a hyperosmolar state. Rigorous perioperative management may obviate some of the infectious and wound-healing complications that are more common in these patients (138). In one study, compulsive control of blood glucose contributed to a decreased overall mortality in myocardial infarction patients (141).

Thyroid Syndromes

Thyroid dysfunction should be suspected in any patient with a history of hyperthyroidism, use of thyroid replacement medication or antithyroid medication, prior thyroid surgery, or radioactive iodine therapy.

Hyperthyroidism

Diffuse toxic goiter (Grave's disease) is the most common cause of hyperthyroidism and results from abnormal stimulation of the thyroid gland by antithyroid antibodies. Any signs or symptoms suggestive of weight loss, tachycardia, atrial fibrillation, goiter, or proptosis should initiate a more extensive laboratory evaluation of thyroid function. Total thyroxin, free T₃, free thyroxin (T₄), and thyroid-stimulating hormone (TSH) tests are useful in diagnosis.

In hyperthyroidism, the free T₄ level will be elevated, and the TSH level will be suppressed (134). A new diagnosis of hyperthyroidism necessitates postponement of elective surgery until adequate treatment with antithyroid medication because of the risk of thyroid storm. **Ideally, an euthyroid state should be maintained for 3 months before elective surgery.** In emergent situations, beta-blockers can be used to counter sympathomimetic drive such as palpitations, diaphoresis, and anxiety. Antithyroid medications such as *propylthiouracil (PTU)* or *radioactive iodine* do not render patients euthyroid quickly enough for urgent surgery. *Radioactive iodine* requires 6 to 18 weeks to establish a euthyroid state (134). When thyroid dysfunction is corrected and maintained for several months, elective surgery can proceed without additional perioperative monitoring. Antithyroid medications should be resumed with return of bowel function. If a prolonged delay in resumption of oral intake is encountered, *PTU* and *methimazole* can

be administered rectally (142). **When time does not permit establishment of a euthyroid state preoperatively, oral administration of PTU and a beta-blocker can be implemented for 2 weeks before surgery, and with careful monitoring, optimal results can be achieved** (140). Alternatively, oral *beta-blockers*, *glucocorticoids*, and *sodium iopanoate* can be used for 5 days, followed by surgery on the day 6 (142). In the emergent setting, however, close monitoring of the patient for tachycardia, arrhythmias, and hypertension is necessary. *Beta-blockers* can control these symptoms until definitive therapy can be initiated after recovery from surgery. Any signs suggestive of the development of thyroid storm—including hemodynamic instability, tachycardia, arrhythmias, hyperreflexia, diarrhea, fever, delirium, or congestive heart failure—mandate transfer to an intensive care setting for optimal monitoring and management in consultation with a medical endocrinologist. Such thyroid instability can be triggered by underlying infection, which requires diagnosis and treatment to facilitate management of this medical emergency. The mortality rate from thyroid storm has been reported to be between 10% and 75% (142). Treatment of thyroid storm consists of *beta-blockers*, *thioamides*, *iodine*, *iodinated contrast agents*, and *corticosteroids* (131). *Aspirin* should not be given for fever in the patient with thyroid storm because it may interfere with the protein binding of T₄ and T₃, resulting in increased free serum concentrations (131).

Hypothyroidism

The incidence of hypothyroidism is approximately 1% in the adult population, and 5% in adults older than 50 years (134). **In women older than 60 years, the incidence of hypothyroidism may approach 6%** (143). **Hypothyroidism is 10 times more common in women than in men** (134). Many such cases are secondary to previous antithyroid

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therapy (*radioactive iodine* or thyroidectomy) for hyperthyroidism. The most common primary cause of hypothyroidism is Hashimoto's thyroiditis, an autoimmune condition (134). A history of lethargy, cold intolerance, lassitude, weight gain, fluid retention, constipation, dry skin, hoarseness, periorbital edema, and brittle hair can be indicative of inadequate thyroid function. In this setting, physical findings of increased relaxation phase of deep tendon reflexes, cardiomegaly, pleural or pericardial effusions, or peripheral edema should stimulate further investigation of thyroid function by assessment of TSH and free T₄ levels.

Hypothyroidism decreases cardiac output by 30% to 50% as a result of decreased stroke volume and heart rate (144). Hyponatremia may also be associated with hypothyroidism because of the inability of the kidney to excrete water (144). When elective surgery is planned for severely hypothyroid patients, surgery should be postponed until thyroid replacement therapy has been initiated (134). In patients with mild or moderate hypothyroidism, the delay of surgery is controversial (134).

For young patients with mild to moderate hypothyroidism, a starting dose of 1.6 µg/kg of thyroid hormone replacement can be given. In elderly patients, *thyroxin* dosage (0.025 mg once a day) should be doubled every 2 weeks until the patient is taking a dose of 0.15 mg daily (143). **Dosage levels can ultimately be titrated against TSH levels.** In severely hypothyroid patients requiring urgent or emergent surgery, intravenous T₃ or T₄ may be given, along with intravenous *corticosteroids* to avoid consequences of unrecognized adrenal insufficiency (131,134).

In the immediate postoperative setting, T₄ therapy can be held for 5 to 7 days while waiting for return of bowel function because the half-life of circulating T₄ is approximately 5 to 9 days (131). If more than 5 to 7 days of decreased bowel function are expected, T₄ can be given by the intramuscular or intravenous route at approximately 80% of the oral dose (143,144).

Adrenal Insufficiency

Adrenal insufficiency may result in catastrophic postoperative complications, including death. The most common cause of adrenal insufficiency in the surgical patient is secondary to the exogenous use of *corticosteroids*. Therefore, the physician should ascertain whether a patient has used exogenous steroids for asthma, malignant conditions, arthritis, or irritable bowel syndrome. The type of steroid use, the route, the dose, the duration, and the temporal relationship to the timing of the surgical procedure must be determined. The type of surgical procedure and its associated stress should also be taken into consideration. The use of high doses of exogenous steroids for prolonged periods can cause circulatory collapse, and they have adverse effects on wound healing and immunocompetence.

The daily replacement dose of cortisol is approximately 5 to 7.5 mg of prednisone. Suppression of the hypothalamic–pituitary–adrenal axis by

exogenous steroids for more than a few weeks may produce relative adrenal insufficiency. When systemic steroids are used for longer periods, adrenal insufficiency may persist for up to 1 year. Short courses of low-dose oral steroids (less than 5 mg of *prednisone* in a single morning dose for any duration of time, alternate-day dosing of short-acting glucocorticoids, and any dose of corticosteroids given for less than 3 weeks) are not thought to cause clinically significant suppression of the hypothalamic–pituitary–adrenal axis (131).

If either the dose or duration of glucocorticoid administration exceeds the preceding regimen, biochemical tests have been recommended to preoperatively evaluate the function of the adrenal gland. The easiest and safest test to assess hypothalamic–pituitary–adrenal function is the cosyntropin stimulation test. *Cosyntropin*, a synthetic analog of adrenocorticotropic hormone, is given in a dose of 250 µg (0.25 mg) intravenously, and a blood sample is collected 30 minutes after the injection and assayed for plasma cortisol. A plasma cortisol value of greater than 18 to 20 µg/dL indicates adequate adrenal function (134). If the history regarding exogenous steroid use is unclear, the cosyntropin stimulation test should

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be considered as a preoperative test to determine if the patient will need perioperative glucocorticoid coverage. The amount of glucocorticoid replacement should be equivalent to the normal physiologic response to surgical stress (Table 20.12) (145).

Table 20.12 Guidelines for Adrenal Supplementation Therapy^a

<i>Medical or Surgical Stress</i>	<i>Corticosteroid Dosage</i>
Minor	
Inguinal hernia repair	25 mg of hydrocortisone or 5 mg of methylprednisolone IV on day of procedure only
Colonoscopy	
Mild febrile illness	
Mild-moderate nausea/vomiting	
Gastroenteritis	
Moderate	

Open cholecystectomy Hemicolectomy Significant febrile illness Pneumonia Severe gastroenteritis	50–75 mg of hydrocortisone or 10–15 mg of <i>methylprednisolone</i> IV on day of procedure Taper quickly over 1–2 days to usual dose
Severe	
Major cardiothoracic surgery Whipple procedure Liver resection Pancreatitis	100–150 mg of <i>hydrocortisone</i> or 20–30 mg of <i>methylprednisolone</i> IV on day of procedure Rapid taper to usual dose over next 1–2 days
Critically Ill	
Sepsis-induced hypotension or shock	50–100 mg of <i>hydrocortisone</i> IV every 6–8 h or 0.18 mg/kg/h as a continuous infusion + 50 µg/d of <i>fludrocortisone</i> until shock resolved. May take several days to a week or more, then gradually taper, following vital signs and serum sodium.
IV, intravenously.	
<p>^aPatients receiving 5 mg/d or less of <i>prednisone</i> should receive their normal daily replacement but do not require supplementation. Patients who receive greater than 5 mg/d of <i>prednisone</i> should receive the above therapy in addition to their maintenance therapy.</p> <p>Reprinted from Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. <i>JAMA</i> 2002;287:236–240, with permission.</p>	

For minor surgical stress, such as colonoscopy, the glucocorticoid target is approximately 25 mg of *hydrocortisone* equivalent on the day of the procedure (145). For moderate surgical stress, for example, open cholecystectomy, the glucocorticoid target is 50 to 75 mg of *hydrocortisone* equivalent on the day of the procedure and tapered quickly for 1 to 2 days (145). The patient should receive her normal daily dose preoperatively, followed by 50 mg of *hydrocortisone* intravenously administered intraoperatively. For major surgical stress, such as liver resection, the glucocorticoid target range is 100 to 150 mg *hydrocortisone* equivalent on the day of the procedure, tapering rapidly over the next 1 to 2 days to the usual dosage (145). The patient should receive her normal daily dose preoperatively.

Administration of high-dose steroids should be stopped as soon as possible postoperatively because they can inhibit wound healing and promote infection. Hypertension and glucose intolerance also can develop. When a prolonged or involved procedure is performed and longer steroid use is necessary, careful tapering may be required. The previously recommended approach was to halve the dose of *hydrocortisone* on a daily basis until a dose of 25 mg is reached. Eliminating one daily dose each day until the drug has been stopped has been considered the safest method of withdrawal; however, no

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consensus on the timing or duration of steroid tapering currently exists. Addison's disease is uncommon but should be considered in the differential diagnosis if the patient develops perioperative hypotension after steroids are withdrawn. In addition to blood and isotonic fluid replacement, a "stress" dose of steroids should be given if adrenal insufficiency is suspected and sepsis and hypovolemia have been excluded.

Cardiovascular Diseases

The incidence of perioperative cardiovascular complications has decreased markedly as a result of improvements in preoperative detection of high-risk patients, preoperative preparation, and surgical and anesthetic techniques (146).

Preoperative Evaluation

The goal of a preoperative cardiac evaluation is to determine the presence of heart disease, its severity, and the potential risk to the patient during the perioperative period. Every patient should be questioned about symptoms of cardiac disease including chest pain, dyspnea on exertion, peripheral edema, wheezing, syncope, claudication, or palpitations. Patients with a history of cardiac disease should be evaluated for worsening of symptoms, which indicates progressive or poorly controlled disease. Records of previous treatment should be obtained. Prescriptions for antihypertensive, anticoagulant, antiarrhythmic, antilipid, or antianginal medications may be the only indication of cardiac problems. In patients without known heart disease, the presence of DM, hyperlipidemia, hypertension, tobacco use, or a family history of heart disease identifies patients at higher risk for heart disease who should be more carefully screened.

On physical examination, the presence of findings such as hypertension, jugular venous distention, laterally displaced point of maximum impulse, irregular pulse, third heart sound, pulmonary rales, heart murmurs, peripheral edema, or vascular bruits should prompt a more complete evaluation. Laboratory evaluation of patients with known or suspected heart disease should include a blood count and serum chemistry analysis. Patients with heart disease tolerate anemia poorly. Serum sodium and potassium levels are particularly important in patients taking diuretics and digitalis. Blood urea nitrogen and creatinine values provide information on renal function and hydration status. Assessment of blood glucose levels may detect undiagnosed DM. Chest radiography and electrocardiography are mandatory as part of the preoperative evaluation, and the results may be particularly helpful when compared with those of previous studies.

Coronary Artery Disease

Coronary artery disease is a major risk factor for patients undergoing abdominal surgery. In an adult population without a prior history of myocardial infarction, the incidence of myocardial infarction following surgery is 0.1% to 0.7% (147). In patients who have had a prior myocardial infarction, however, the reinfarction rate is 2.8% to 7% (148). The risk of reinfarction is inversely proportional to the length of time between infarction and surgery. At 3 months or less, the risk of reinfarction is 5.7%, and from 3 to 6 months, the rate falls to 2.3%. Six months after myocardial infarction, the reinfarction rate is 1.5% (147). Fortunately, careful perioperative management can lower the reinfarction rate even in patients who have had recent infarctions. Perioperative myocardial infarction is associated with a mortality rate of 26% to 70% (149).

Because of the high mortality and morbidity associated with perioperative myocardial infarction, much effort has been made to predict perioperative cardiac risk. **A prospective evaluation of preoperative cardiac risk factors using a multivariate analysis identified independent cardiac risk factors for patients undergoing noncardiac surgery (149).** Using these factors, a cardiac risk index was created that placed a patient in one of four risk classes. This cardiac risk index was then further modified and validated prospectively, resulting in the most current tool for clinical risk assessment in nonemergent major

noncardiac surgery, the Revised Cardiac Risk Index (150). Risk factors include high-risk surgical procedures, history of ischemic heart disease, history of congestive heart failure, history of transient ischemic attack or stroke, preoperative insulin therapy, and preoperative serum creatinine levels greater than 2.0 mg/dL. Depending on the number of risk factors, the risk of major cardiac events (myocardial infarction, cardiac arrest, pulmonary edema, and complete heart block) range from 0.5% to 9.1% (Table 20.13).

Table 20.13 Major Cardiac Event Rates by the Revised Cardiac Risk Index

Class	(number of risk factors)	Events/Patient	Event Rate% (95% CI)
I	(0)	2/488	0.4 (0.05, 1.5)
II	(1)	5/567	0.9 (0.3, 2.1)
III	(2)	17/258	6.6 (3.9, 10.3)
IV	(3)	12/109	11.0 (5.8, 18.4)

CI, confidence interval.

Adapted from **Lee TH, Marcantonio ER, Mangione CM, et al.** Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043–1049.

Risk assessment is stratified into three major categories: (i) clinical predictors, (ii) functional capacity, and (iii) surgery-specific risk (151). Clinical predictors of increased perioperative cardiac risk are divided into major, intermediate, and minor factors (Table 20.14). The patient's functional status is assessed by a thorough history (Table 20.15), and self-reported exercise tolerance can be used to predict perioperative risk (152). **Patients with**

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poor functional capacity have higher perioperative cardiac risk and should be considered for preoperative cardiac function testing (148). Surgery-specific risk is subdivided into high-risk procedures (emergent major operations, aortic and vascular procedures, and prolonged surgical procedures associated with large fluid shifts or blood loss), intermediate-risk procedures (other intraperitoneal operations),

and low-risk procedures (endoscopic surgery, breast surgery, and superficial procedures).

Table 20.14 Clinical Predictors of Increased Perioperative Cardiovascular Risk

Major

Unstable coronary syndromes (acute or recent MI, unstable or severe angina)
 Decompensated congestive heart failure
 Significant arrhythmias (high-grade AV block, symptomatic ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate)
 Severe valvular disease

Intermediate

Mild angina
 Prior myocardial infarction (more than 1 month before planned surgery)
 Compensated or prior congestive heart failure
 Diabetes mellitus
 Renal insufficiency

Minor

Advanced age
 Abnormal ECG (LVH, LBBB, ST-T abnormalities)
 Rhythm other than sinus
 Low functional capacity
 History of stroke
 Uncontrolled systemic hypertension

MI, myocardial infarction; AV, atrioventricular; ECG, electrocardiogram; LVH, left ventricular hypertrophy; LBBB, left bundle branch block.

Adapted from **Eagle KA, Berger PB, Calkins H, et al.** ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2002; 105: 1257–1267.

Table 20.15 Functional Capacity Assessment from Clinical History

Excellent

Carry 24 lb up eight steps
 Carry objects that weigh 80 lb
 Outdoor work (shovel snow, spade soil)
 Recreation (ski, basketball, squash, handball, jog or walk 5 mph)

Moderate

Have sexual intercourse without stopping
 Walk at 4 mph on ground level
 Outdoor work (garden, rake, weed)
 Recreation (roller-skate, dance)

Poor

Shower and dress without stopping
 Basic housework
 Walk 2.5 mph on level ground
 Recreation (golf, bowl)

Adapted from **Mehta RH, Bossone E, Eagle KA**. Perioperative cardiac risk assessment for noncardiac surgery. *Cardiologia* 1999;44:409–418.

In an effort to quantitate preoperative cardiac risk, several tests have been used to assess cardiovascular function. **Exercise stress testing before surgery can identify patients who have ischemic heart disease not apparent at rest.** These patients have been shown to be at increased risk of developing cardiac complications in the perioperative period. In a study of patients undergoing peripheral vascular surgery, a high-risk group of patients was identified who had ischemic electrocardiographic changes when they exercised to less than 75% of their maximal predicted heart rate. In this group, the incidence of perioperative myocardial infarction was 25%, and the overall cardiac mortality rate was 18.5%. Conversely, no perioperative infarctions occurred in patients who were able to exercise to more than 75% of their maximal predicted heart rate and who had no electrocardiographic evidence of ischemia (153). However, the prognostic value of stress testing was not supported in another prospective study that found that only an abnormal preoperative resting electrocardiography result was an independent risk factor (154). The exercise stress test must be selectively applied to a high-risk population because its predictive

value depends on the prevalence of the disease. Therefore, it is not prudent to screen all patients preoperatively; it is preferable to rely on a careful history to identify patients with symptoms of cardiac disease for whom the test would be most predictive.

Exercise stress testing is limited in some patients who cannot exercise because of musculoskeletal disease, pulmonary disease, or severe cardiac disease. *Dipyridamole-thallium scanning* may be used to overcome the limitations of exercise stress testing. This study has a high degree of sensitivity and specificity, and it relies on the ability of *dipyridamole* to dilate normal coronary arteries but not stenotic vessels. Normally perfused myocardium readily takes up *thallium* when it is given intravenously. Conversely, hypoperfused myocardium does not show good uptake of *thallium* when scanned 5 minutes after injection. Reperfusion and uptake of *thallium* 3 hours after injection identify viable but high-risk

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myocardium. Old infarctions are identified as areas without uptake. Several studies have shown a risk of perioperative myocardial infarction in patients with areas of reperfusion of *thallium* uptake ranging from 20% to 33% (155,156). The *dipyridamole-thallium* scan is applicable to patients who are unable to exercise because it uses a medically induced "stress."

Dobutamine stress echocardiography is another test to evaluate cardiac risk in patients who are unable to exercise. This method identifies regional cardiac wall motion abnormalities after *dobutamine* infusion to identify patients at high risk for cardiac events. Positive and negative predictive values are similar to those of *dipyridamole-thallium* testing (157,158). Coronary angiography should be considered only in patients who have an indication for angiography independent of the planned surgery, such as patients with acute coronary syndromes, unstable angina, angina refractory to medical therapy, or high-risk results on noninvasive testing.

Preoperative testing should be used discriminately in intermediate-risk patients. Controversy exists regarding the accuracy of these tests to provide prognostic information beyond what is obtained from clinical risk stratification for nonvascular procedures. Diagnostic testing should not lead to unnecessary additional testing or harmful delays in surgery. **The American College of Cardiology and the American Heart Association present an updated detailed algorithm that incorporates risk-factor stratification to guide clinicians to proceed directly to surgery, obtain noninvasive testing, consider coronary angiography, or consider delay of surgery and risk-factor modification** (151).

It is rare for patients who are younger than 50 years and who do not have diabetes, hypertension, hypercholesterolemia, or coronary artery disease to suffer a perioperative myocardial infarction. However, patients with coronary artery disease are at increased risk of myocardial infarction in the postoperative period. Prevention, early recognition, and treatment are important because myocardial infarctions that occur in the postoperative period have mortality rates of approximately 50% and are more lethal than those that are not associated with surgery.

Nearly two thirds of postoperative myocardial infarctions occur during the first 3 days postoperatively. Although the pathophysiologic factors are complex, the causes of postoperative myocardial ischemia and infarction are related to decreased myocardial oxygen supply coupled with increased myocardial oxygen requirements. In postoperative patients, conditions that decrease oxygen supply to the myocardium include tachycardia, increased preload, hypotension, anemia, and hypoxia (159). Conditions that increase myocardial oxygen consumption are tachycardia, increased preload, increased afterload, and increased contractility. Tachycardia and increased preload are the most important causes of ischemia, because both conditions decrease oxygen supply to the myocardium while simultaneously increasing myocardial oxygen demand. Tachycardia decreases the diastolic time, which, when the coronary arteries are perfused, decreases the volume of oxygen available to the myocardium. Increased preload increases the pressure exerted by the myocardial wall on the arterioles within it, thus decreasing myocardial blood flow.

Other factors associated with perioperative myocardial ischemia include physiologic responses to the stress of intubation, intravenous or intra-arterial line placement, emergence from anesthesia, pain, and anxiety. This stress results in catecholamine stimulation of the cardiovascular system, resulting in increased heart rate, blood pressure, and contractility, which may induce or worsen myocardial ischemia. Loss of intravascular volume because of third spacing of fluids or postoperative hemorrhage can also induce ischemia.

Postoperative myocardial infarction is often difficult to diagnose. Chest pain, which is present in 90% of nonsurgical patients with myocardial infarction, may be present in only

50% of patients with postoperative infarction because myocardial pain may be masked by coexisting surgical pain and the use of analgesia (147). Thus, it is important to maintain a high

level of suspicion for postoperative infarction in patients with coronary artery disease. The presence of arrhythmia, congestive heart failure, hypotension, dyspnea, or elevations of pulmonary artery pressure may indicate infarction and should prompt a thorough cardiac investigation and electrocardiographic monitoring. **Measurement of creatinine phosphokinase myocardial band (CPK-MB) isoenzyme and troponin T levels are the most sensitive and specific indicators of myocardial infarction, and assessments should be obtained for all patients suspected of myocardial infarction.**

Despite the high incidence of silent myocardial infarction, routine use of postoperative electrocardiography (ECG) for all patients with cardiovascular disease is controversial. Many patients will exhibit P-wave changes that spontaneously resolve and do not represent ischemia or infarction. Conversely, patients with proven myocardial infarctions may show few, if any, ECG abnormalities. Currently, the American College of Cardiology and American Heart Association recommend postoperative surveillance of perioperative myocardial infarction in patients with known or suspected coronary artery disease (151). A recent study of patients older than 50 years undergoing major noncardiac surgery found that immediate postoperative ECG may be a valuable tool in patients who have lower risks when undergoing major noncardiac surgery (160). However, this is a preliminary study, and further investigation is warranted. If routine screening of asymptomatic patients is desired, ECG should be performed 24 hours following surgery because significant ECG changes that occur immediately postoperatively will persist for 24 hours. It is prudent to continue serial ECG assessments for at least 3 days postoperatively.

Postoperative management of patients with coronary artery disease is based on maximizing delivery of oxygen to the myocardium as well as decreasing myocardial oxygen utilization. Most patients benefit from supplemental oxygen in the postoperative period, although special care should be exercised in patients with COPD. Oxygenation can easily be monitored by pulse oximetry. Anemia is detrimental because of loss of oxygen-carrying capacity as well as resultant tachycardia and should, therefore, be carefully corrected in high-risk patients.

Patients with coronary artery disease may benefit from pharmacologic control of hyperadrenergic states that result from increased postoperative catecholamine production. Beta-blockers decrease heart rate, myocardial contractility, and systemic blood pressure, all of which are increased by adrenergic stimulation. Perioperative

use of β_1 selective beta-blocker has been shown to significantly reduce perioperative ischemia, myocardial infarction, and overall mortality caused by cardiac death and congestive heart failure in the perioperative period (161,162,163). Perioperative beta-blocker therapy is recommended for patients with at least two of the following minor risk factors: age 65 years or older, hypertension, current smoker, serum cholesterol at least 240 mg/dL, or DM not requiring *insulin* therapy (162). Therapy also is recommended for patients having any one of the risk factors defined by the Revised Cardiac Risk Index (150). The timing and optimal duration of beta-blocker therapy remains an area of uncertainty. Current evidence suggests initiating therapy at least 1 week before surgery and continuing throughout the hospitalization. For patients receiving beta-blockade therapy before surgery, therapy should be continued in the perioperative period because abrupt withdrawal results in a rebound hyperadrenergic state.

Although prophylactic nitrates have been used in the perioperative period for many years, this practice remains controversial. *Nitroglycerin* enhances blood flow to ischemic areas, increases collateral flow, increases myocardial oxygenation, and reduces angina (164,165,166,167). The route of administration, dosage, and duration of therapy are controversial; thus, perioperative treatment with nitrates should be initiated in consultation with a cardiologist. Likewise, calcium-channel blockers have not proved useful in the prophylaxis of perioperative myocardial ischemia (168).

Congestive Heart Failure

Patients with congestive heart failure (CHF) face a substantially increased risk of myocardial infarction during and after surgery (149). The postoperative development of pulmonary edema is a grave prognostic sign and results in death in a high percentage of patients (169). Because patients with heart failure at the time of surgery are significantly more likely to develop pulmonary edema perioperatively, every effort should be made to diagnose and treat CHF before surgery (170). The signs and symptoms of CHF are listed in Table 20.16 and should be assessed based on preoperative history and physical examination. Patients who are able to perform usual daily activities without developing CHF are at limited risk of perioperative heart failure.

Table 20.16 Signs and Symptoms of Congestive Heart Failure

- | |
|---|
| 1. Presence of an S ₃ gallop |
| 2. Jugular venous distention |
| 3. Lateral shift of the point of maximal impulse |
| 4. Lower-extremity edema |
| 5. Basilar rales |
| 6. Increased voltage on electrocardiogram |
| 7. Evidence of pulmonary edema or cardiac enlargement on chest radiograph |
| 8. Tachycardia |

To prevent severe postoperative complications, CHF must be corrected

preoperatively. Treatment usually relies on aggressive diuretic therapy, although care must be taken to avoid dehydration, which may result in hypotension during the induction of anesthesia. Hypokalemia can result from diuretic therapy and is especially deleterious to patients who are also taking digitalis. In addition to diuretics and *digitalis*, treatment often includes the use of preload- and afterload-reducing agents. Optimal use of these drugs and correction of CHF may be aided by consultation with a cardiologist. In general, it is preferable to continue the usual regimen of cardioactive drugs throughout the perioperative period.

Postoperative CHF results most frequently from excessive administration of intravenous fluids and blood products.

Other common postoperative causes are myocardial infarction, systemic infection, pulmonary embolism, and cardiac arrhythmias. The cause of postoperative heart failure must be diagnosed because, to be successful, treatment should be directed simultaneously to the underlying cause. Postoperative diagnosis of CHF is often more difficult than preoperative diagnosis because the signs and symptoms of CHF are not specific and may result from other causes. The most reliable method of detecting CHF is chest radiography, in which the presence of cardiomegaly or evidence of pulmonary edema is a helpful diagnostic feature.

Acute postoperative CHF frequently manifests as pulmonary edema. Treatment of

pulmonary edema may include the use of intravenous *furosemide*, supplemental oxygen, *morphine sulfate*, and elevation of the head of the bed. Intravenous *aminophylline* may be useful if cardiogenic asthma is present. Electrocardiography, in addition to laboratory evaluation, including arterial blood gas, serum electrolyte, and renal function chemistry measurements, should be obtained expediently. If the patient's condition does not improve rapidly, she should be transferred to an intensive care unit.

Arrhythmias

Nearly all arrhythmias found in otherwise healthy patients are asymptomatic and of limited consequence. In patients with underlying cardiac disease, however, even

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brief episodes of arrhythmias may result in significant cardiac morbidity and mortality.

Preoperative evaluation of arrhythmias by a cardiologist and anesthesiologist is important because many anesthetic agents as well as surgical stress contribute to the development or worsening of arrhythmias. In patients undergoing continuous electrocardiographic monitoring during surgery, a 60% incidence of arrhythmias, excluding sinus tachycardia, has been reported (171). **Patients with heart disease have an increased risk of arrhythmias, most commonly ventricular arrhythmias** (171). Conversely, patients without cardiac disease are more likely to develop supraventricular arrhythmias during surgery. Patients taking antiarrhythmic medications before surgery should continue taking those drugs during the perioperative period. Initiation of antiarrhythmic medications is rarely indicated preoperatively, but consultation with a cardiologist is recommended for patients in whom arrhythmias are detected before surgery.

Patients with first-degree atrioventricular (AV) block or asymptomatic Mobitz I (Wenckebach) second-degree AV block require no preoperative therapy. Conversely, a pacemaker is appropriate in patients with symptomatic Mobitz II second- or third-degree AV block before elective surgery (172). In emergency situations, a pacing pulmonary artery catheter can be used. Before performing surgery on patients with a permanent pacemaker, the type and location of the pacemaker should be determined because electrocautery units may interfere with demand-type pacemakers (173). **When performing gynecologic surgery on patients with pacemakers, it is preferable to place the electrocautery unit ground plate on the leg**

to minimize interference. In patients with a demand pacemaker in place, the pacemaker should be converted preoperatively to the fixed-rate mode.

Surgery is not contraindicated in patients with bundle branch blocks or hemiblocks. Complete heart block rarely develops during noncardiac surgical procedures in patients with conduction system disease (174,175,176). However, the presence of a left bundle branch block may indicate the presence of aortic stenosis, which can increase surgical mortality if it is severe.

Valvular Heart Disease

Although there are many forms of valvular heart disease, primarily two types—aortic and mitral stenosis—are associated with significantly increased operative risk (177). Patients with significant aortic stenosis appear to be at greatest risk, which is further increased in the presence of atrial fibrillation, congestive heart failure, or coronary artery disease. Significant stenosis of aortic or mitral valves should be repaired before elective gynecologic surgery (148).

Severe valvular heart disease usually is evident during physical exertion. Common findings in such patients are listed in Table 20.17. The classic history presented by patients with severe aortic stenosis includes exercise dyspnea, angina, and syncope, whereas symptoms of mitral stenosis are paroxysmal and effort dyspnea, hemoptysis, and orthopnea. Most patients have a remote history of rheumatic fever. Severe stenosis of either valve is considered to be a valvular area of less than 1 cm², and diagnosis can be confirmed by echocardiography or cardiac catheterization.

Table 20.17 Signs and Symptoms of Valvular Heart Disease

Aortic stenosis

1. Systolic murmur at right sternal border, which radiates into carotids
2. Decreased systolic blood pressure
3. Apical heave
4. Chest radiograph with calcified aortic ring, left ventricular enlargement
5. Electrocardiogram with high R waves, depressed T waves in lead I, and precordial leads

Mitral stenosis

1. Precordial heave
2. Diastolic murmur at apex
3. Mitral opening snap
4. Suffused face and lips
5. Chest radiograph with left atrial dilation
6. Electrocardiogram with large P waves and right axis deviation

Patients with valvular abnormalities have been subdivided by the American Heart Association into risk groups for the development of subacute bacterial endocarditis following surgery (61). Patients with prosthetic valves are classified as high risk, whereas patients with mitral valve prolapse with regurgitation, history of rheumatic heart disease, or bicuspid aortic valve are considered at moderate risk. **Patients in both high- and moderate-risk groups should receive prophylactic antibiotics immediately preoperatively to prevent subacute bacterial endocarditis** (see Table 20.7).

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Patients with aortic and mitral stenosis tolerate sinus tachycardia and other tachyarrhythmias poorly. In patients with aortic stenosis, sufficient levels of *digitalis* should be provided to correct preoperative tachyarrhythmias, and *propranolol* may be used to control sinus tachycardia. Patients with mitral valve stenosis often have atrial fibrillation and, if present, *digitalis* should be used to reduce rapid ventricular response.

Patients with mechanical heart valves usually tolerate surgery well (178). These patients should receive antibiotic prophylaxis (see Table 20.7), and anticoagulant therapy should be discontinued during the perioperative period. If the patient is taking *aspirin* therapy, it should be discontinued 1 week before the procedure and restarted as soon as it is considered safe by

the surgeon. Usually, *warfarin* (*Coumadin*) is withheld 72 hours before surgery, and anticoagulation is obtained by intravenous administration of *heparin* once the INR falls below 2.0 (179,180). *Heparin* is discontinued 6 to 8 hours before surgery and resumed when the risk of bleeding is low and continued until the patient is returned to *warfarin* maintenance therapy (180,181). Alternatively, *warfarin* can be stopped 72 hours before the procedure and restarted within 24 hours of the procedure (182). **The American College of Cardiology and American Heart Association Guidelines recommend perioperative heparinization in patients who have more thrombogenic valves, recent thrombosis, or embolus (arbitrarily within 1 year); those with more than three of the following risk factors: atrial fibrillation, previous thromboembolism, hypercoagulable condition, and mechanical prosthesis; or those with one risk factor and a mechanical valve in the mitral position** (180). Both methods of management have essentially no risk of thromboembolic complications and bleeding complication rates of approximately 15%.

In the postoperative period, patients with mitral stenosis should be carefully monitored for pulmonary edema because they may not be able to compensate for the amount of intravenous fluid administered during surgery. Patients with mitral stenosis also frequently have pulmonary hypertension and decreased airway compliance. Therefore, they may require more pulmonary support and therapy postoperatively, including prolonged mechanical ventilation.

For patients with significant aortic stenosis, it is imperative that a sinus rhythm be maintained during the postoperative period. Even sinus tachycardia can be deleterious

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because it shortens the diastolic time. Bradycardia less than 45 beats per minute should be treated with *atropine*. Supraventricular dysrhythmias may be controlled with *verapamil* or direct-current cardioversion. Particular attention should be provided to the maintenance of proper fluid status, digoxin levels, electrolyte levels, and blood replacement.

Hypertension

Patients with controlled essential hypertension have no increased risk of perioperative cardiac morbidity or mortality (170). However, patients with concomitant heart disease are at elevated risk and should be completely evaluated by a cardiologist preoperatively. Laboratory studies should include an ECG, chest radiography,

blood count, urinalysis, and serum electrolytes and creatinine measurement.

Antihypertensive medications should be continued perioperatively. Of note, beta-blockers should be continued, parenterally if necessary, to avoid rebound tachycardia, hypercontractility, and hypertension.

Patients with diastolic pressures higher than 110 mm Hg or systolic pressures higher than 180 mm Hg should receive medication to control their hypertension before surgery. Chronically hypertensive patients are very susceptible to intraoperative hypotension because of impaired autoregulation of blood flow to the brain and, therefore, require a higher mean arterial pressure to maintain adequate perfusion (183). Conversely, during induction of anesthesia, episodes of hypertension occur, and such episodes are seen more frequently in patients with baseline hypertension.

Postoperative hypertension is usually treated parenterally because gastrointestinal absorption may be diminished, and transdermal absorption can be erratic in patients who are cold and rewarming. Commonly used parenteral antihypertensives are listed in Table 20.18.

Table 20.18 Common Parenteral Antihypertensives

<i>Drug</i>	<i>Route</i>	<i>Initial Dose</i>	<i>Onset</i>	<i>Duration</i>	<i>Side Effects</i>
<i>Nitroprusside</i>	IV infusion	0.5 µg/min	Immediate	2–5 min	Tachycardia, nausea
<i>Labetalol</i>	IV infusion	20 mg	5–10 min	4 h	Bronchospasm, dizziness, nausea
<i>Esmolol</i>	IV infusion	50 µg/min	2 h	9 min	Headache, somnolence, dizziness, hypotension
<i>Nifedipine</i>	Sublingual	10 mg	5 min	2 min	Hypotension, headache, dizziness, nausea, peripheral edema
<i>Verapamil</i>	IV infusion	5–10 mg	3–5 min	2–5 h	Nausea, headache, hypotension, dizziness, pulmonary edema
IV, intravenous.					

Hemodynamic Monitoring

Hemodynamic monitoring has become integral to the perioperative management of patients

with cardiovascular and pulmonary disease. The major impetus for this advancement resides in the need for the quantitative estimate of cardiac function, resulting in the development of bedside pulmonary artery catheterization. The impact of monitoring of cardiac function is demonstrated by the significant reduction of myocardial infarctions in high-risk patients who are aggressively monitored for 72 to 96 hours postoperatively (147).

Before the development of the pulmonary artery catheter, central venous pressure (CVP) measurement was used to assess intravascular volume status and cardiac function. To measure the CVP, a catheter is placed in the central venous system, most frequently the superior vena cava. A water manometer or a calibrated pressure transducer is connected to the CVP line, thus allowing an estimation of right atrial pressure to be obtained. Right atrial pressure is determined by the balance between cardiac output and venous return.

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Cardiac output is determined by heart rate, myocardial contractility, preload, and afterload. Thus, if the pulmonary vascularity and left ventricular function are normal, the CVP accurately reflects the left ventricular end-diastolic pressure (LVEDP). The LVEDP reflects cardiac output or systemic perfusion and has been considered the standard estimator of left ventricular pump function. Venous return is determined primarily by the mean systemic pressure, which propels blood toward the heart, balanced against resistance to venous return, which acts in the opposite direction. Thus, if right ventricular function is normal, the CVP accurately reflects intravascular volume.

Left and right ventricular function is frequently abnormal or discordant; therefore, the relationship of CVP to cardiac function and to intravascular volume is not maintained. When this occurs, measurement of pulmonary artery occlusion pressure is required to accurately assess volume status and cardiovascular function. The use of a pulmonary artery catheter also allows detection of changes in cardiovascular function with more sensitivity and rapidity than clinical observation.

The balloon-tipped pulmonary artery catheter (Swan-Ganz catheter) can measure pulmonary artery and pulmonary artery occlusion pressures (184). The catheter can measure cardiac output, be used to perform intracavitary electrocardiography, and provide temporary cardiac pacing. The standard pulmonary artery occlusion catheter is a 7-French, radiopaque, flexible, polyvinyl chloride, 4-lumen catheter with a 1.5-mL latex balloon at its distal tip. Most often, a

right internal jugular cannulation is used for placement of the catheter, because this site provides the most direct access into the right atrium and has fewer complications when compared with a subclavian route of placement. After the catheter is placed into the right atrium, the balloon is inflated, and the catheter is pulled by blood flow through the right ventricle into the pulmonary artery. The position of the catheter can be identified and followed by the various pressure waveforms generated by the right atrium, right ventricle, and pulmonary artery. As the catheter passes through increasingly smaller branches of the pulmonary artery, the inflated balloon eventually occludes the pulmonary artery.

The distal lumen of the catheter, which is beyond the balloon, measures left atrial pressure (LAP) and, in the absence of mitral valvular disease, LAP approximates LVEDP. Thus, pulmonary–capillary wedge pressure (PCWP) equals the LAP, which equals LVEDP and is normal at 8 to 12 mm Hg. Additionally, because the standard pulmonary artery catheter has an incorporated thermistor, thermodilution studies can be performed to determine cardiac output. This thermodilution method is performed by injecting cold 5% dextrose in water through the proximal port of the catheter, which cools the blood entering the right atrium. The change in temperature measured at the more distal thermistor (4 cm from the catheter tip) generates a curve proportional to cardiac output. Knowledge of the cardiac output is helpful in establishing cardiovascular diagnoses. For example, a patient with hypotension, low-to-normal wedge pressure, and a cardiac output of 3 L/minute is most likely hypovolemic. Conversely, the same patient with a cardiac output of 8 L/minute is probably septic with resultant low systemic vascular resistance.

Pulmonary artery catheters are associated with a small but significant complication rate. The complications can be grouped into those occurring during venous cannulation and those resulting from the catheter or its placement. The most common problems encountered during venous access are cannulation of the carotid or subclavian artery and introduction of a pneumothorax. Problems resulting from the catheter itself include dysrhythmias, sepsis, and disruption of the pulmonary artery. Pulmonary artery catheters should be placed under the supervision of experienced personnel in a setting in which complications can be rapidly diagnosed and treated.

The effect of pulmonary artery catheter use on patient outcome has become controversial. In 1996, a reevaluation of pulmonary artery catheters and initiation of randomized clinical

trials to assess their benefit was recommended (185). At that time, others published a large study demonstrating a higher mortality rate in patients who received a pulmonary artery catheter than those that did not have a pulmonary artery catheter (186). The design of this study was questionable, however, and it was retrospective and not randomized. A meta-analysis evaluating 12 randomized clinical trials showed a statistically significant reduction in morbidity (63% versus 74%, $P < 0.01$) in the pulmonary artery catheter group, but no significant difference in mortality (187). Finally, in a recent randomized blinded controlled trial of 1,994 high-risk (American Society of Anesthesiologists class III or IV risk) subjects 60 years of age or older undergoing urgent or elective major noncardiac surgery, therapy guided by pulmonary artery catheters showed no benefit over standard care with central venous catheters (188). Therefore, **routine preoperative use of pulmonary artery catheters in noncardiac surgery patients is no longer indicated.**

Hematologic Disorders

The presence of hematologic disorders, although uncommon in gynecologic patients, significantly affects operative morbidity and mortality and, therefore, should be considered routinely in preoperative evaluation. Preoperative assessment should include consideration of anemia, platelet and coagulation disorders, white blood cell function, and immunity.

Anemia

Moderate anemia is not in itself a contraindication to surgery because it can be corrected by transfusion. If possible, surgery should be postponed until the cause of the anemia can be identified and the anemia corrected without resorting to transfusion. **Current anesthetic and surgical practice ideally recommend a hemoglobin level of greater than 10 g/dL or a hematocrit of greater than 30%. Such numbers are only guidelines and should be applied on an individual basis.** Oxygen-carrying capacity and tissue oxygenation is provided by the circulating blood volume. Usually this capacity is reflected by the hemoglobin level and hematocrit. Under certain circumstances, however, this is not the case. After an acute blood loss or before plasma expansion by extracellular fluid has occurred, hematocrit measurements may be normal despite a low circulating blood volume.

Conversely, overhydration may result in low hematocrit and hemoglobin levels despite adequate

red blood cell mass.

Individual tolerance of anemia depends on overall physical fitness and cardiovascular reserve. The effects of anemia depend on its magnitude, the rate at which it occurs, the oxygen requirement of the patient, and the ability of physiologic mechanisms to compensate (189). Maintenance of adequate tissue perfusion requires an increase in cardiac output as hemoglobin concentration falls (190). A patient with ischemic heart disease will not tolerate anemia as well as a healthy young patient. Therefore, the presence of cardiac, pulmonary, or other serious illness justifies a more conservative approach to the management of anemia. Conversely, patients with long-standing anemia may have normal blood volume levels and tolerate surgical procedures well. There is no evidence that mild to moderate anemia increases perioperative morbidity or mortality (191).

Patients with normal hematocrit levels may store three or more units of autologous blood preoperatively to reduce the need for allogenic blood transfusion and minimize the risk of infections and immunologic problems (192). *Recombinant human erythropoietin* may increase collection and reduce preoperative anemia in these patients (193,194). Further, intraoperative blood collection and homologous transfusion can be employed to limit the need for allogenic blood transfusion.

Autologous blood donation has been advocated as a safer alternative for the patient; however, the use of preoperative autologous blood donation has come under scrutiny (195).

Preoperative autologous blood may lead to more liberal blood transfusion, iatrogenic anemia, volume overload, and bacterial contamination (196). Furthermore,

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preoperative autologous blood donation is poorly cost-effective (197). The National Heart, Lung, and Blood Institute does not recommend collection of autologous blood for procedures with a likelihood of transfusion less than 10%, such as uncomplicated abdominal and vaginal hysterectomies (198).

Platelet and Coagulation Disorders

Surgical hemostasis is provided by platelet adhesion to injured vessels, which plugs the opening as the coagulation cascade is activated, resulting in the formation of fibrin clots. Thus, functional platelets and coagulation pathways are necessary to prevent excessive surgical

bleeding. Platelet dysfunction is encountered preoperatively more frequently than coagulation disorders.

Platelets may be deficient in both number and function. The normal peripheral blood count is 150,000 to 400,000 per mm^3 , and the normal life span of a platelet is approximately 10 days. Although there is no clear-cut correlation between the degree of thrombocytopenia and the presence or amount of bleeding, several generalizations can be made. If the platelet count is higher than $100,000/\text{mm}^3$ and the platelets are functioning normally, there is little chance of bleeding during surgical procedures. Patients with a platelet count higher than $75,000/\text{mm}^3$ almost always have normal bleeding times, and a platelet count higher than $50,000/\text{mm}^3$ is probably adequate. **A platelet count lower than $20,000/\text{mm}^3$ will often be associated with severe and spontaneous bleeding.** Platelet counts higher than $1,000,000/\text{mm}^3$ are often, paradoxically, associated with bleeding.

If the patient's platelet count is lower than $100,000/\text{mm}^3$, an assessment of bleeding time should be obtained. If the bleeding time is abnormal and surgery must be performed, an attempt should be made to raise the platelet count by administering platelet transfusions immediately before surgery. In patients with immune destruction of platelets, human leukocyte antigen (HLA)-matched donor-specific platelets may be required to prevent rapid destruction of transfused platelets. If surgery can be postponed, a hematology consultation should be obtained to identify and treat the cause of the platelet abnormality.

Abnormally low platelet counts result from either decreased production or increased consumption of platelets. Although there are numerous causes of thrombocytopenia, most are exceedingly uncommon. Decreased platelet production may be drug induced and has been associated with the use of *sulfonamides, cinchona alkaloids, thiazide diuretics, NSAIDs, gold salts, penicillamine, anticonvulsants, and heparins* (199). Decreased platelet count is a feature of several diseases, including vitamin B₁₂ and folate deficiency, aplastic anemia, myeloproliferative disorders, renal failure, and viral infections. Inherited congenital thrombocytopenia is extremely rare. More commonly, thrombocytopenia results from immune destruction of platelets by diseases such as idiopathic thrombocytopenia purpura and collagen vascular disorders. **Consumptive thrombocytopenia is a feature of disseminated intravascular coagulation, which is encountered most frequently in conjunction with sepsis or malignancy in the preoperative population.**

Platelet dysfunction most often is acquired, but may be inherited. Occasionally, a patient with von Willebrand's disease, the second most common inherited disorder of coagulation, may be encountered in the preoperative setting. More commonly, however, platelet dysfunction results from the use of drugs (e.g., *aspirin* and *amitriptyline*), and in patients with resulting prolonged bleeding times. the drug should be withheld for 7 to 10 days before surgery. Uremia and hepatic diseases can also affect platelet function.

Platelet dysfunction is more difficult to diagnose than abnormalities of platelet count. A history of easy bruising, petechiae, bleeding from mucous membranes, or prolonged bleeding from minor wounds may signify an underlying abnormality of platelet function. Such dysfunction can be identified with the help of a bleeding time, but full characterization of

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the underlying etiology should be carried out with hematologic consultation. If at all possible, surgery should be postponed until therapy has been instituted.

Similarly, disorders of the coagulation cascade often are diagnosed through a personal or family history of excessive bleeding during minor surgery, childbirth, or menses. Many women with menorrhagia are referred for surgical intervention and require a thorough preoperative evaluation for possible inherited disorders of hemostasis, such as factor VIII (hemophilia), factor IX (Christmas disease), factor XI deficiencies, and von Willebrand's disease. Von Willebrand's disease is the most common hereditary bleeding disorder, with prevalence in the general population of 0.8% to 1.3% (200,201). In women with menorrhagia, the prevalence of von Willebrand's disease increases to 13% to 20% (202,203). Identified women can potentially be treated effectively with *desmopressin* nasal spray, thus avoiding unanticipated or excessive bleeding during surgery. In the absence of a genetic diagnosis, the diagnosis of von Willebrand's disease is difficult and involves a combination of clinical and laboratory assessments, including von Willebrand factor antigen and von Willebrand factor functional activity or ristocetin cofactor assay. Physiologic fluctuations occur with von Willebrand factor levels, requiring repeat testing and consultation or referral to a hematologist. Nevertheless, it is recommended that women presenting with menorrhagia without obvious pelvic abnormalities should be routinely screened for inherited bleeding disorders before undergoing invasive procedures.

There are few commonly prescribed drugs that affect coagulation factors, the exceptions being *warfarin* and *heparin*. Disease states that may be associated with decreased coagulation

factor levels are primarily liver disease, vitamin K deficiency (secondary to obstructive biliary disease, intestinal malabsorption, or antibiotic reduction of bowel flora), and disseminated intravascular coagulation.

Preoperative laboratory screening for coagulation deficiencies is controversial. Routine screening is not warranted in patients who do not have historical evidence of a bleeding problem (204). However, patients who are seriously ill or who will be undergoing extensive surgical procedures should undergo testing preoperatively to determine prothrombin time, partial thromboplastin time, fibrinogen level, and platelet count.

White Blood Cells and Immune Function

Abnormally high or low white blood cell counts are not an absolute contraindication to surgery; however, they should be considered relative to the need for surgery. Evaluation of an elevated or decreased white blood cell count should be undertaken before elective surgery. Clearly, **patients with absolute granulocyte counts lower than 1,000/mm³ are at increased risk of severe infection and perioperative morbidity and mortality and should undergo surgery only for life-threatening indications** (205).

Blood Component Replacement

Most hematologic problems observed in the postoperative period are related to perioperative bleeding and blood component replacement. Although the primary cause of the bleeding is usually lack of surgical hemostasis, other factors, including deranged coagulation, may compound the problem. Such coagulopathy can result from massive transfusion (less than one blood volume) and is thought to be due to dilution of platelets and labile coagulation factors by platelet- and factor-poor packed red blood cells (PRBCs), fibrinolysis, and disseminated intravascular coagulation.

Reports of massive transfusions in soldiers reveal that for those in whom thrombocytopenia developed following red blood cell replacement, bleeding diatheses that responded to infusion of fresh blood but not fresh-frozen plasma (FFP) also developed (206). The investigators concluded that dilutional thrombocytopenia is a major cause of posttransfusion bleeding. However, more recently, in a prospective, randomized, double-blind study, prophylactic platelet administration during massive transfusion was not helpful (207).

Although it seems that these studies are contradictory, they demonstrate the need for obtaining platelet counts during transfusion of large amounts of blood. If clinical evidence of excessive bleeding exists and the platelet count is lower than $100,000/\text{mm}^3$, platelets should be transfused because they are consumed during surgery, and higher levels are required to maintain hemostasis following surgery.

Packed red blood cells, which may be stored for several weeks, are used for most postoperative transfusions. Most clotting factors are stable for long periods. The exceptions are factors V and VIII, which decrease to 15% and 50% of normal, respectively. Despite this loss, these factors rarely decrease below levels required for hemostasis. In 1985, a National Institutes of Health consensus conference concluded that there was little or no scientific evidence to support the use of FFP for bleeding diatheses following multiple blood transfusions except in the presence of clinical bleeding, platelet count higher than $100,000/\text{mm}^3$, and a partial thromboplastin time greater than 1.5 times control. A task force of the American Society of Anesthesiologists (208) recently **recommended critical values for replacement in patients with massive transfusion and microvascular bleeding:**

- **Platelet transfusion usually is indicated for counts less than $50,000/\text{mm}^3$ (with intermediate platelet counts, i.e., $50,000/\text{mm}^3$ - $100,000/\text{mm}^3$, the transfusion of platelet concentrates should be based on the risk of more significant bleeding).**
- **Fresh frozen plasma therapy is indicated if the prothrombin or activated partial thromboplastin time values exceed 1.5 times the normal values.**
- **Cryoprecipitate transfusion is indicated if fibrinogen concentrations decrease to less than 80 to 100 mg/dL.**

Cryoprecipitate transfusions are recommended for prophylaxis in nonbleeding perioperative

patients with fibrinogen deficiencies or von Willebrand's disease refractory to *DDAVP*, and bleeding patients with von Willebrand's disease (208).

Donor blood is stored in the presence of citrate, which chelates calcium to prevent clotting, increasing the theoretical risk of hypocalcemia following massive transfusion. However, citrate is metabolized at a rate equivalent to 20 units of blood transfused per hour; thus, routine supplementation of calcium is unnecessary. Close monitoring of calcium levels is required in patients with hypothermia, liver disease, or hyperventilation because citrate metabolism may be slowed. Hepatic metabolism of citrate to bicarbonate can result in metabolic alkalosis following transfusion, resulting in subsequent hypokalemia, despite the high level of extracellular potassium in stored blood.

Pulmonary Disease

In patients undergoing abdominal surgery, several pulmonary physiologic changes manifest secondary to immobilization, anesthetic irritation of the airways, and the splinting of breathing that inevitably occurs secondary to incisional pain. Pulmonary physiologic changes include a decrease in the functional residual capacity (FRC), an increase in ventilation perfusion mismatching, and impaired mucociliary clearance of secretions from the tracheobronchial tree (209). In multivariate regression analyses, **definite risk factors for postoperative pulmonary complications include the following** (210):

- **Upper abdominal, thoracic, or abdominal aortic aneurysm surgery**
- **Surgical procedure time longer than 3 hours**
- **American Society of Anesthesiologists class greater than 2**
- **Previous COPD**

Smoking within 2 months of surgery

•

Use of *pancuronium* for general anesthesia

Probable risk factors include general anesthesia, preoperative PaCO₂ greater than 45 mm Hg, and emergency surgery. Risk factors that could possibly increase the postoperative risk are upper respiratory infection, abnormal chest x-ray, and elderly age (older than 70 years). Preoperative spirometry is of unproven value in patients in whom the risk of postoperative pulmonary complications is low. In high-risk patients, preoperative spirometry should be performed with and without bronchodilators to identify patients who may benefit from preoperative treatment with inhaled β_2 agonists and steroids.

These patients include those with a history of chronic cough or dyspnea, evidence of pulmonary abnormalities by either physical examination or chest x-ray, and a history of COPD, as well as patients with a significant history of smoking. The spirometric abnormalities most often associated with postoperative atelectasis and pneumonia are shown in Table 20.19. Reduction of the forced expiratory volume in 1 second (FEV 1) is an important parameter to note on pulmonary function tests (209). The routine performance of preoperative arterial blood gas measurements does not improve assessment of risk (209). Noninvasive pulse-oximetry measurements can detect patients with hypoxemia (209). The presence of hypercarbia on arterial blood gas measurements also does not predict postoperative pulmonary complications (211).

Table 20.19 Predictors of Postoperative Pulmonary Complications^a

<i>Parameter</i>	<i>Value</i>
Maximal breathing capacity	<50% predicted
FEV ₁	<1 L
FVC	<70% predicted
FEV ₁ /FVC	<65% predicted
Pao ₂	<60 mm Hg
Paco ₂	>45 mm Hg

^a*Complication* defined as atelectasis or pneumonia.

FEV₁, forced expiration volume; FVC, forced vital capacity; Pao₂, partial pressure of oxygen, arterial; Paco₂, partial pressure of carbon dioxide, arterial.

Adapted from **Blosser SA, Rock P.** Asthma and chronic obstructive lung disease. In: **Breslow MJ, Miller CJ, Rogers MC,** eds. *Perioperative management*. St. Louis, MO: Mosby, 1990:259–280.

Young, healthy patients rarely have abnormal chest x-rays. Therefore, chest x-rays should not be performed routinely in these patients. Most patients with abnormal chest x-rays have history or physical examination findings suggestive of pulmonary disease. Chest x-rays should be limited to patients older than 40 years of age, with a history of smoking or of pulmonary disease, who have evidence of cardiopulmonary disease, and in whom a metastatic malignancy is suspected. Although they have limited usefulness in predicting postoperative pulmonary complications, chest x-rays provide a valuable baseline in elderly patients, patients with chronic pulmonary diseases (209), and those with known lung metastases.

Asthma

Asthma affects approximately 5% to 7% of individuals in the United States (212). It is characterized by a history of episodic wheezing, physiologic evidence of reversible obstruction of the airways either spontaneously or following bronchodilator therapy, and pathologic evidence of chronic inflammatory changes in the bronchial submucosa. Asthma is not a disease of airway physiology in which hypertrophy and increased contractility of bronchial smooth muscle is the dominant lesion; rather, it is an inflammatory disease

affecting the airways that secondarily results in epithelial damage, leukocytic infiltration, and increased sensitivity of the airways to a number of different stimuli. The treatment of asthma is directed toward relaxing the airways and alleviating inflammation with corticosteroids (212).

Multiple stimuli have been noted to precipitate or exacerbate asthma, including environmental allergens or pollutants, respiratory tract infections, exercise, cold air, emotional stress, nonselective beta-adrenergic blockers, and aspirin (213). Management of asthma includes removal of the inciting stimuli as well as use of appropriate pharmacologic therapy. The optimal therapy for asthma involves not only managing the acute symptoms but also long-term management of the inflammatory component of the disease.

Pharmacotherapy of Asthma

The recognition of asthma as an inflammatory condition that should be treated with anti-inflammatory agents has led to the use of corticosteroids for treatment. Because corticosteroids inhibit mediator release from eosinophils and macrophages, inhibit the late response to allergens, and reduce hyperresponsiveness of the bronchioles, they have become the first-line therapy for chronic asthma (214). **Inhaled steroids have greatly reduced the steroid dose required to achieve optimal results.** The steroid effect is dose related, but many patients with asthma can achieve control using low-dose inhaled steroids. Onset of action is slow (several hours), and up to 3 months of steroid therapy may be required for optimal improvement of bronchial hyperresponsiveness. Even with acute bronchospasm, steroid treatment can enhance the beneficial effect of beta-adrenergic treatment. During acute exacerbations of asthma, a short course of oral steroids, in addition to inhaled steroids, may be necessary. For adults with chronic asthma, however, only a minority will require chronic oral steroid therapy. Patients taking oral steroids should receive intravenous steroid support perioperatively to avoid adrenal insufficiency.

Beta₂-adrenergic agonists remain the first-line drugs for acute asthma attacks.

These drugs, inhaled 4 to 6 times daily, rapidly relax smooth muscle in the airways and are effective for up to 6 hours. Studies of beta₂ agonists in chronic asthma, however, have failed to show any influence of these agents on the inflammatory component of asthma. Furthermore,

it has been suggested that the long-term use of this class of drugs can lead to a worsening of asthma (214). Thus, beta₂ agonists are now recommended for use for short-term relief of bronchospasm ("rescue inhalers") or as first-line treatment for patients with very infrequent symptoms or symptoms provoked solely by exercise (215).

Methylxanthines, such as *theophylline*, have been relegated to third-line status in the management of asthma. It is doubtful whether these drugs have any additional benefit in patients who are using maximal inhaler therapy. *Theophylline* toxicity can develop when other drugs such as *ciprofloxacin*, *erythromycin*, *allopurinol*, *inderal*, or *cimetidine* are concomitantly administered (212).

Anticholinergic agents are weak bronchodilators that work via inhibition of muscarinic receptors in the smooth muscle of the airways. The quaternary derivatives such as *ipratropium bromide* (*Atrovent*) are available in an inhaled form that is not absorbed systemically. Anticholinergic drugs may provide additional benefit in conjunction with standard steroid and bronchodilator therapy but should not be used as single-agent therapy because they do not inhibit mast cell degranulation, do not have any effect on the late response to allergens, and do not have an anti-inflammatory effect.

Cromolyn sodium is highly active in the treatment of seasonal allergic asthma in children and young adults. It is usually not as effective in older patients or in patients in whom asthma is not allergic in nature (215). The drug is taken by inhalation but has a relatively

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short duration of action (3–4 hours). It has a mild anti-inflammatory effect but is less effective than inhaled cortical steroids, and its role as a single agent is limited.

Perioperative Management of Asthma

In patients with asthma, elective surgery should be postponed whenever possible until pulmonary function and pharmacotherapeutic management are optimized.

The preoperative evaluation may include pulmonary function testing and arterial blood gases depending on the severity of the symptoms and concern regarding ventilation and oxygenation. Preoperative chest physiotherapy, bronchodilator therapy, systemic hydration, and appropriate antibiotics will improve the reversible components of asthma (216). For

mild asthma, the use of inhaled beta-adrenergic agonists preoperatively may be all that is required. For chronic asthma, optimization of steroid therapy will greatly decrease alveolar inflammation and bronchiolar hyperresponsiveness. Inhaled beta₂ agonists should be added to therapy as needed for further control of asthma. Each drug prescribed should be used in maximal dosage before adding an additional agent. For patients undergoing emergent surgery who have significant bronchoconstriction, a multimodal approach should be instituted, including aggressive bronchodilator inhalation therapy, intravenous *aminophylline*, as well as steroid therapy. Ideally, steroid therapy can be instituted 3 to 6 days preoperatively. In all patients with asthma, pharmacotherapeutic response can be monitored with pulmonary function testing as demonstrated by an improvement in the peak expiratory flow rate (215).

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is the greatest risk factor for the development of postoperative pulmonary complications. The term *COPD* has been used to encompass both chronic bronchitis and emphysema, disease entities that often occur in tandem. Cigarette smoke is implicated in the pathogenesis of both, and any treatment plan must include cessation of smoking (217). Chronic bronchitis is defined as the presence of productive cough on most days for at least 3 months per year and for at least 2 successive years (218). It is characterized by chronic airway inflammation and excessive mucus production. The histologic changes of emphysema include destruction of alveolar septa and distension of airspaces distal to terminal alveoli. The destruction of alveoli results in air trapping, loss of pulmonary elastic recoil, collapse of the airways in expiration, increased work of breathing, significant ventilation-perfusion mismatching, and an ineffective cough (219). The impaired ability to cough effectively and clear secretions predisposes patients with COPD to atelectasis and pneumonia in the postoperative period.

Patients with COPD and a history of heavy smoking account for most postoperative pulmonary complications in gynecologic surgical patients. The severity of COPD can be determined preoperatively via a thorough history, physical examination, pulmonary function tests, and arterial blood gas assessment. Preoperative evaluation should be performed to assess reversible components of COPD, such as bronchospasm or infection.

The severity of COPD can be quantitated with pulmonary function testing (217). Typically,

forced expiratory volume (FEV_1), forced vital capacity (FVC), FEV_1/FVC . In patients considered to be at high risk, the incidence of complications was highest in those undergoing abdominal surgery (92%) or thoracic surgery (78%) and lowest in those undergoing surgery outside the abdomen (26%). The current American College of Physicians guidelines list the following indications for preoperative spirometry: lung resection; coronary artery bypass or upper abdominal surgery in a patient with a positive smoking history or dyspnea; and lower abdominal surgery in a patient with uncharacterized pulmonary symptoms or history of pulmonary disease without recent spirometry within 60 days, especially if the surgery will be extensive, prolonged, or require strenuous postoperative rehabilitation (220).

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Older data suggest that arterial blood gas measurements may show varying degrees of hypoxemia and hypercapnia and can be used for prognostic purposes; PaO_2 levels lower than 70 mm Hg and $PaCO_2$ levels higher than 45 mm Hg are associated with an increase in the risk of postoperative pulmonary complications and the need for mechanical ventilation postoperatively (221). $PaCO_2$ levels higher than 50 mm Hg are associated with increased postoperative respiratory failure and should caution against elective surgery (216).

The preoperative preparation of the patient at risk for postoperative pulmonary complications should include cessation of smoking for as long as possible preoperatively; whereas 2 to 3 days of smoking abstinence are sufficient for carboxyhemoglobin levels to return to normal (209). One to two weeks of cessation decreases sputum volume (209). Two months of smoking abstinence is required to significantly lower the risk of postoperative pulmonary complications (209). Longer periods of abstinence can thus be counseled in patients undergoing elective surgery.

In patients with severe COPD, maximum improvement in airflow limitation can be achieved with a therapeutic trial of high-dose oral corticosteroids followed by a 2-week trial of high-dose inhaled steroid (*beclomethasone* 1.5 mg/day or the equivalent) in addition to inhaled bronchodilator therapy. Ideally, oral and inhaled steroid therapy should be initiated 1 to 2 weeks preoperatively. Inhaled steroids, in particular, address the inflammatory component of COPD. Oral steroid therapy initiated preoperatively should be maintained throughout the perioperative period and then tapered postoperatively. Beta-adrenergic agonist therapy can

be initiated at least 72 hours preoperatively and is beneficial in patients who have demonstrated either clinical or spirometric improvement on bronchodilators.

Patients with COPD and an active bacterial infection suggested by purulent sputum should undergo a full course of antibiotic therapy before surgery. The antibiotic used should cover the most likely etiologic organisms, *Streptococcus pneumoniae* and *Haemophilus influenzae*. In any patient with acute upper respiratory infection, surgery should be delayed if possible. The use of antibiotics to sterilize the sputum in the absence of evidence of an acute infection should be avoided because this practice may lead to bacterial resistance.

Instruction in deep breathing maneuvers and chest physical therapy are easily instituted, and these measures can be started the evening before surgery (222). These prophylactic measures (smoking cessation, pharmacotherapies, and aggressive pulmonary toilet) should be instituted preoperatively and continued postoperatively to minimize the incidence of atelectasis and pneumonia.

Postoperative Pulmonary Management

Atelectasis

Atelectasis accounts for more than 90% of all postoperative pulmonary complications.

The pathophysiology involves a collapse of the alveoli, resulting in ventilation-perfusion mismatching, intrapulmonary venous shunting, and a subsequent drop in the PaO₂. Collapsed alveoli are susceptible to superimposed infection, and if managed

improperly, atelectasis will progress to pneumonia. Patients with atelectasis have a decreased FRC as well as decreased lung compliance, resulting in increased work during breathing. Despite the decrease in PaO₂, the PCO₂ remains unaffected unless atelectatic changes progress to large volumes of the lung or pre-existing lung disease is present.

Physical findings associated with atelectasis may include a low-grade fever. Auscultation of the chest may reveal decreased breath sounds at the bases or dry rales upon inspiration. Percussion of the posterior thorax may suggest elevation of the diaphragm.

Radiologic findings include the presence of horizontal lines or plates on posteroanterior chest x-rays, occasionally with adjacent areas containing hyperinflation. These changes are most pronounced during the first 3 postoperative days.

Therapy for atelectasis should be aimed at expanding the alveoli and increasing the FRC. The most important maneuvers are those that promote maximal inspiratory pressure, which is maintained for as long as possible. This exercise promotes not only an expansion of the alveoli but also secretion of surfactant, which stabilizes alveoli. It can be achieved with aggressive supervised use of incentive spirometry, deep breathing exercises, coughing, and in some cases, the use of positive expiratory pressure with a mask (continuous positive airway pressure). Oversedation should be avoided, and patients should be encouraged to ambulate and change positions frequently. Fiberoptic bronchoscopy for removal of mucopurulent plugs should be reserved for patients who fail to improve with the usual measures.

Cardiogenic (High-Pressure) Pulmonary Edema

Cardiogenic pulmonary edema can result from myocardial ischemia, myocardial infarction, or from intravascular volume overload, particularly in patients who have low cardiac reserve or renal failure. The process usually begins with an increase in the fluid in the alveolar septa and bronchial vascular cuffs, ultimately seeping into the alveoli. Complete filling of the alveoli impairs secretion and production of surfactant. Concomitant with alveolar flooding, there is a decrease in lung compliance, impairment of the oxygen diffusion capacity, and an increase in the arteriolar–alveolar oxygen gradient. Ventilation-perfusion mismatching in the lung results in a decrease in the PaO_2 , resulting eventually in decreased oxygenation of the tissues and impairment of cardiac contractility.

Symptoms may include tachypnea, dyspnea, wheezing, and use of the accessory muscles of respiration. Clinical signs may include distention of the jugular veins, peripheral edema, rales upon auscultation of the lungs, and an enlarged heart. Radiographic findings may include the presence of bronchiolar cuffing, as well as increased interstitial fluid markings extending to the periphery of the lung. The diagnosis can be further confirmed with the use of central hemodynamic monitoring, which will denote an elevated central venous pressure and, more specifically, an elevation in the pulmonary capillary wedge pressure.

The patient's volume status should be evaluated thoroughly. In addition, myocardial ischemia

or infarction should be ruled out by performing ECG and analyzing cardiac enzyme levels. The management of cardiogenic pulmonary edema includes oxygen support, aggressive diuresis, and afterload reduction to increase the cardiac output. In the absence of myocardial infarction, an inotropic agent may be used. Mechanical ventilation should be reserved for cases of acute respiratory failure.

Noncardiogenic Pulmonary Edema (Adult Respiratory Distress Syndrome)

In contrast with cardiogenic pulmonary edema, in which alveolar flooding is a result of an increase in the hydrostatic pressure of the pulmonary capillaries, alveolar flooding in patients with adult respiratory distress syndrome (ARDS) is the result of an increase in pulmonary capillary permeability. The primary pathophysiologic process is one of damage to the capillary side of the alveolar–capillary membrane. This damage results in rapid movement of fluid containing high concentrations of protein from the capillaries to the pulmonary parenchyma and alveoli. Lung compliance decreases and oxygen diffusion capacity is impaired, resulting in hypoxemia. If not managed aggressively, respiratory failure may result. Even when managed aggressively, the mortality rate

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associated with ARDS is high. There are a number of causes as well as several distinct states of ARDS. **The causes of ARDS include shock, sepsis, massive nonlung trauma (as from fractures or burns), multiple red blood cell transfusions, aspiration injury, inhalation injury, pneumonia, pancreatitis, disseminated intravascular coagulation, and fat emboli** (216). Irrespective of the cause, which should be identified and treated if possible, the evolving clinical picture and management are very similar.

Clinically, ARDS passes through several stages. Initially, patients develop tachypnea and dyspnea with no remarkable findings on clinical evaluation or on chest x-ray. Chest x-rays will eventually reveal bilateral diffuse pulmonary infiltrates. As lung compliance becomes impaired, functional residual capacity, tidal volume, and vital capacity decrease. The PaO₂ decreases and, characteristically, increases only marginally with oxygen supplementation. An attempt should be made to maintain the arterial oxygen level above 90%. This may be achievable initially by administering oxygen by mask. For patients with severe

hypoxemia, endotracheal intubation with positive-pressure ventilation should be instituted. Guidelines for initial ventilatory support are changing, and new lung-protective ventilation strategies are being advocated. One strategy advocates the use of high positive end-expiratory pressure (PEEP), low tidal volume, permissive hypercapnia, and pressure-limited ventilatory modes. The low tidal volume strategy may confer a survival advantage, and available data support its use in patients with ARDS (223). Multicenter ARDSNet trials are currently under way to assess differences in PEEP and FIO₂ levels and the use of corticosteroids. Analysis of a recent ARDSNet trial found no difference in the application of high or low levels of PEEP, holding tidal volume and end-inspiratory pressure stable at 30 cm of water (224). Attempts to manage and treat the cause of ARDS must also include aggressive efforts toward hemodynamic and circulatory resuscitation in patients with shock. Nosocomial pneumonia is present in 50% of patients with ARDS, and broad-spectrum antibiotic therapy should be administered appropriately for patients with suspected pneumonia or sepsis. Patients who have disseminated intravascular coagulopathy may require replacement with cryoprecipitate or FFP. Other measures for general care should include the placement of a nasogastric tube, gastric acid suppression with H₂ blockers, and administration of steroids in patients with the fat emboli syndrome.

Hemodynamic monitoring is invaluable and should be initiated early in the course of the disease process in the appropriate intensive care unit setting. Patients with any evidence of fluid overload should receive aggressive diuresis, whereas others may require fluid resuscitation for maintenance of tissue perfusion while the pulmonary-capillary wedge pressure is maintained below 15 mm Hg. Pulmonary wedge pressure may be falsely elevated when PEEP is being applied. The goal of management is to maintain the lowest pulmonary-capillary wedge pressure, with acceptable cardiac output and blood pressure. In the setting of hypotension and oliguria, inotropic support with dopamine or dobutamine or both is helpful.

With aggressive management, particularly if the inciting cause is identified and treated, ARDS can be reversed during the first 48 hours with few sequelae. After the first 48 hours, however, progression of the ARDS will cause lung damage that may leave residual pulmonary fibrosis. With progression beyond 10 days, multiorgan system failure occurs, and mortality is higher than 80% (223).

Renal Disease

The need for surgical intervention in patients with renal impairment has resulted in the development of a very specialized medical approach to their care. Special precautions are necessary to compensate for the kidney's impaired ability to regulate fluids and electrolytes and excrete metabolic waste products. Equally important are the unique problems that develop in patients with chronic renal impairment, including an increased risk of sepsis, coagulation defects, impaired immune function and wound healing, and a

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propensity to develop specific acid-base abnormalities. Special consideration must be given to a variety of different medications, anesthetic agents, and numerous hematologic and nutritional factors that are important in the successful surgical care of patients with renal insufficiency.

Management of fluid levels and cardiovascular hemodynamics in patients with acute or chronic renal impairment is paramount. Intravascular fluid volume changes that lead to hypertension or hypotension are very common in these patients and often are difficult to manage secondary to autonomic dysfunction, acidosis, and other problems that are inherent to the underlying kidney disease. Patients undergoing dialysis in whom major abdominal or pelvic surgery is contemplated should be treated using a Swan-Ganz catheter intraoperatively and postoperatively. The results of physical examination and CVP monitoring correlate poorly with left cardiac filling pressures. Swan-Ganz catheter measurements will help guide fluid replacement and avoid volume overload. Invasive hemodynamic monitoring should be continued as needed throughout the first postoperative week because third spacing will occur during this period.

Postoperative dialysis usually is necessary to avoid problems associated with fluid overload and hyperkalemia. Dialysis-dependent patients should undergo dialysis approximately 24 hours following surgery. A short-lived but rather significant fall in the number of platelets occurs during dialysis, and *heparin* is used in hemodialysis equipment to prevent clotting. Because of these factors and concerns about postoperative bleeding, dialysis is usually avoided during the first 12 to 24 hours following surgery. Although ischemic heart disease is the most common cause of death in patients with renal insufficiency, it is not a major cause of perioperative mortality (225). A large percentage of perioperative deaths of patients with renal insufficiency are associated with hyperkalemia that is controlled most

Patients with chronic renal failure are at an increased risk for postoperative infections resulting from abnormalities in neutrophil and monocyte function (227). Appropriate preoperative antibiotic prophylaxis and accurate assessment of nutritional status help lower the incidence of postoperative infectious complications.

The major hematologic concern in patients with chronic renal insufficiency is the increased incidence of bleeding. These bleeding problems are secondary to abnormal bleeding times and, in particular, disorders of platelet function related to a decreased amount of factor VIII and von Willebrand antigen in the serum of uremic patients. Anemia, which is common in patients with renal insufficiency, can contribute to prolonged bleeding times (228). Abnormalities in arachidonic acid metabolism, acquired platelet storage pool deficiency, and disturbed regulation of platelet calcium content all contribute to an increased tendency for uremic patients to have significant bleeding during surgery (229). Therefore, the bleeding time should be routinely checked preoperatively in these patients, and abnormalities should be corrected before surgery. Options for the correction of bleeding time in uremic patients include infusion of *desmopressin* or *cryoprecipitate*, both of which act to increase plasma levels of factor VIII and von Willebrand antigen (230,231).

Normal renal function is essential for maintenance of acid-base balance in the body. Patients with renal insufficiency can have a normal anion gap or an elevated anion gap acidosis. When mild renal insufficiency develops, a normal anion gap is present, whereas in more significant and severe renal dysfunction, an elevated anion gap acidosis occurs. Hemodialysis corrects metabolic acidosis. If a patient is severely acidotic (pH <7.15) and emergency surgery is planned, correction of the blood pH to 7.25 using intravenous *sodium bicarbonate* is indicated. However, correction of metabolic acidosis should be carried out slowly, because in patients with hypocalcemia, seizures may be precipitated (231). It is also important to exclude other causes of elevated anion gap acidosis, such as ketoacidosis

secondary to diabetes, lactic acidosis secondary to infection, or in rare instances, poisoning with *ethylene glycol*, *methanol*, or *aspirin*.

Impaired kidney function causes phosphate retention by the kidney and impaired vitamin D metabolism. Therefore, hypocalcemia is common in patients with renal insufficiency, but tetany and other signs of hypocalcemia are relatively uncommon because metabolic

acidosis increases the level of ionized calcium. Oral phosphate binders, such as *aluminum hydroxide* (1–2 g per meal), and dietary phosphate restriction (1 g per day) is the usual treatment for hypocalcemia–hyperphosphatemia in patients with renal insufficiency. In chronic situations, because of central nervous system toxicity associated with elevated aluminum levels, it is preferable to treat hypocalcemia–hyperphosphatemia with large doses of *calcium carbonate* (6–12 g per day) rather than with the standard aluminum-containing antacids (232).

Approximately 20% of patients with renal insufficiency will exhibit clinical evidence of protein calorie malnutrition. Vitamin deficiencies, most notably with water-soluble vitamins, also occur with dialysis. Nutritional disturbances in patients with chronic renal insufficiency arise secondary to deficiencies in protein intake, and studies have shown that, in patients with chronic renal insufficiency, their kidneys are hyperfiltrating (233). Postoperatively, both protein and caloric intake may need to be increased dramatically to meet catabolic demands in surgical patients. As much as 1.5 g/kg of protein and 45 kcal/kg of calories may be needed (233).

Wound healing is impaired in patients with chronic renal failure, and wound dehiscence and evisceration are potential problems. Wound healing is most appropriately aided by nutritional assessment preoperatively and maintenance of adequate caloric and protein intake in the perioperative setting. Antibiotic prophylaxis should be used in these patients, and uremia should be treated with dialysis as indicated. A running mass-closure of the midline vertical incision with continuous monofilament sutures should be used to further decrease the risk of wound dehiscence and evisceration (234).

Patients with chronic renal disease have an altered ability to excrete drugs and are prone to significant metabolic derangements secondary to the altered bioavailability of many commonly used medications. Because of this, as well as the effect of dialysis on drug pharmacokinetics, the gynecologic surgeon and nephrologist must be aware of the lowered metabolism and bioavailability of narcotics, barbiturates, muscle relaxants, antibiotics, and other drugs that require renal clearance. Of particular note is the inability of patients with renal insufficiency to clear the neuromuscular blockade caused by *pancuronium* (235). Care must be taken with *D-tubocurarine*, especially if repeated doses are given (236). *Midazolam*, *propofol*, *vecuronium*, and *atracurium* have been used safely in patients with renal failure (231). *Succinylcholine* has been reported to cause significant hyperkalemic responses in

patients with renal failure (237). When *succinylcholine* is used in patients with chronic renal insufficiency, careful monitoring of the serum potassium level is necessary (238).

Perioperative acute renal failure in previously normal patients may be caused by decreased renal perfusion, nephrotoxins, or both. Patients with impaired cardiac function, intravascular volume depletion, sepsis, or hypotension fall under the first category. Nephrotoxic medications such as *aminoglycosides*, chemotherapeutic agents such as *cisplatin*, or iodinated contrast agents fall under the second category (239,240,241). The risk of renal impairment becomes cumulative if more than one of these factors exist at the same time, and especially if a variety of factors are associated with intervascular volume depletion (242). Several measurements should be used to avoid acute renal failure. All nephrotoxic drugs should be discontinued when possible. When it is not practical to withdraw medication, strict attention should be paid to the pharmacokinetic characteristics of each drug as well as to the regular measurements of serum creatinine levels. Patients with diabetes should be

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given reduced doses of radiocontrast agents and should be well hydrated because they are particularly susceptible to renal injury from these materials (243). Volume repletion is essential to lower the incidence of renal impairment (244).

Liver Disease

Management of perioperative problems in gynecologic patients with liver disease requires a comprehensive understanding of normal liver physiology and the pathophysiology underlying diseases of the liver that may complicate surgery or recovery. **Patients with liver disease often have numerous complicated problems involving nutrition, coagulation, wound healing, encephalopathy, and infection.**

History and Physical Examination

Patients with a history of alcohol abuse, drug use, hepatitis, jaundice, blood product exposure, or a family member with liver disease should undergo biochemical evaluation. During the physical examination, note should be made of any jaundice, signs of muscle wastage, ascites, right upper quadrant tenderness, or hepatomegaly.

Laboratory Testing

The biochemical profile (alkaline phosphatase, calcium, lactic acid dehydrogenase, bilirubin, serum glutamic-oxaloacetic transaminase, cholesterol, uric acid, phosphorous, albumin, total protein, and glucose) has not been shown to be useful for routine preoperative evaluation (245). Mild abnormalities can result in further extensive testing that requires consultation, delays in surgery, and increased cost without net benefit. A possible exception is selected use of biochemical testing when the history or physical examination reveals abnormalities. Patients with known liver disease should undergo albumin and bilirubin testing using the Child's risk classification (Table 20.20). This system was originally designed to predict mortality following portosystemic shunt surgery. It divides patients into three classes of severity based on five easily assessed clinical parameters. Measurement of prothrombin time may also be helpful in patients with significant histories of liver disease. If a history of hepatitis is ascertained, the patient should be tested for serum aminotransferase, alkaline phosphatase, bilirubin, and albumin levels. Serologic documentation of hepatitis is also important. If a patient has a known malignancy, biochemical testing of the liver may be of some benefit as a screen for metastatic disease, although this has not been proved conclusively.

Table 20.20 Child's Classification of Liver Dysfunction

<i>Parameter</i>	<i>Child Classification</i>		
	<i>A</i>	<i>B</i>	<i>C</i>
<i>Bilirubin</i>	<2.0	2.0–3.0	>3.0
<i>Albumin</i>	>3.5	3.0–3.5	<3.0
<i>Ascites</i>	None	Easily controlled	Poor controlled
<i>Encephalopathy</i>	None	Mild	Advanced
<i>Nutritional status</i>	Excellent	Good	Poor

Anesthesia

With few exceptions, most anesthetic agents, including those administered by epidural or spinal routes, reduce hepatic blood flow and decrease oxygenation of the liver. Other perioperative factors—hemorrhage, intraoperative hypotension, hypercarbia, congestive heart failure, and intermittent positive pressure ventilation, especially in critically ill patients—lead to decreased hepatic perfusion and hypoxia (246).

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Drug Metabolism

Patients with altered liver function should be carefully monitored because of the prolonged action of many medications used during surgery. In addition to impaired metabolism, hypoalbuminemia decreases drug binding, which alters serum levels and biliary clearance rates. The degree of hepatic metabolism varies greatly, depending on the type of medication being considered. For inhalation anesthetics, *isoflurane* is preferred because it undergoes minimal hepatic metabolism in comparison with *halothane* or *enflurane*. Narcotics, induction agents, sedatives, and neuromuscular blocking agents all undergo abnormal metabolism in patients with decompensated liver disease. *Diazepam*, *meperidine*, and *phenobarbital* cause prolonged depression of consciousness and may precipitate hepatic encephalopathy because of their altered rates of clearance. *Sufentanil* and *oxazepam* are the preferred narcotics, and *benzodiazepine* should be used for patients with altered liver function. Muscle relaxants, such as *D-tubocurarine*, *pancuronium*, and *vecuronium*, cause prolonged neuromuscular blockade in patients with impaired liver function and are not ideal drugs to use in this situation. *Atracurium* is not metabolized by the liver and, therefore, is the preferred muscle relaxant for patients with abnormal hepatic function. *Succinylcholine* metabolism is prolonged in patients with hepatic dysfunction and must be used with great caution (247).

Determination of Operative Risk

Although it is well known that acute hepatobiliary damage results in increased morbidity and mortality in the surgical patient, estimating the operative risk in patients with hepatic dysfunction is difficult based on the history and physical examination. **The most**

accurate method for risk assessment of surgery in patients with hepatic dysfunction is Child's classification (see Table 20.20). Using this system, accurate assessment of morbidity and mortality can be directly related to the degree of liver dysfunction (248). The Child's classification has been shown to be useful for patients undergoing a variety of different types of abdominal surgery. Operative mortalities of 10%, 31%, and 76% have been reported for each of the three Child's classifications, respectively (249). The major cause of perioperative death was sepsis. This classification correlated significantly with postoperative complications such as bleeding, renal failure, wound dehiscence, and sepsis.

Acute Viral Hepatitis

Acute viral hepatitis poses an increased risk of operative complications and perioperative mortality and, therefore, elective surgery is contraindicated (250).

Elective surgery should be delayed for approximately 1 month after the results of all biochemical tests have returned to normal (251). In patients with ectopic pregnancy, hemorrhage, or bowel obstruction secondary to malignancy, however, surgical intervention must take place before normalization of serum transaminase levels (250). In these situations, the perioperative morbidity (12%) and mortality (9.5%) rates are much higher than when they are performed under ideal situations (247).

Chronic Hepatitis

Chronic hepatitis is a group of disorders characterized by inflammation of the liver for at least 6 months. The disease is divided by morphologic and clinical criteria into chronic persistent hepatitis and chronic active hepatitis. A liver biopsy is usually required to establish the extent and type of injury. The surgical risk in these patients correlates most closely with the severity of disease. The risk of surgery in patients with asymptomatic or mild disease is minimal in contrast to a significant risk for those patients who have symptomatic chronic active hepatitis (252). Elective surgery is contraindicated in symptomatic patients, and nonelective surgery is associated with significant morbidity (251). In the nonelective situation, patients taking long-term *glucocorticoid* therapy should be given appropriate stress coverage with a higher dose of *glucocorticoids* during the perioperative period. Preoperatively, patients who are not taking steroids should receive *prednisone* and *azathioprine*, which have been shown to reduce the perioperative

risk of complications and may result in remission in as many as 80% of patients (253). More recently, a controlled randomized trial of *prednisone* and *interferon- α* has shown regression of the hepatitis B (HBV) core antigen and HBV viral DNA replication in approximately 30% of patients (254). Current strategies for treating chronic HBV also include the use of nucleoside analogs such as *lamivudine* and *adefovir* (255,256). *Pegylated interferon* and *ribavirin* are used in the standard treatment of hepatitis C (HCV) (257). Consideration should be given to using these medications for patients in whom surgery cannot be avoided but is not emergent.

Asymptomatic carriers of the HBV (individuals who test positive for the HBV surface antigen) are not at increased risk for postoperative complications in the absence of elevated aminotransferase levels and liver inflammation. There is, however, a significant risk to the health care professional operating on these individuals. In cases of needlestick in which the patient's hepatitis status is unknown, both the health care worker and the patient should be tested for HCV antibody and HBV serologic markers. If markers for HBV infection are present, *hepatitis B immune globulin* should be administered to unvaccinated medical personnel. A vaccination series should then be initiated during the early postoperative period. If the health care worker is immune (surface antibody positive), no treatment is necessary (247). All medical personnel, and especially those in the surgical subspecialties, should receive a full course of recombinant hepatitis B vaccine as recommended by the Centers for Disease Control and Prevention (258).

Alcoholic Liver Disease

Alcoholic liver disease encompasses a spectrum of diseases including fatty liver, acute alcoholic hepatitis, and cirrhosis. Elective surgery is not contraindicated in patients with fatty liver because liver function is preserved. **If nutritional deficiencies are discovered, they should be corrected before elective surgery.** Acute alcoholic hepatitis is characterized on biopsy by hepatocyte edema, polymorphonuclear leukocyte infiltration, necrosis, and the presence of Mallory bodies. Elective surgery in these patients is contraindicated (259). Abstinence from alcohol for approximately 6 to 12 weeks along with clinical resolution of the biochemical abnormalities are recommended before surgery is considered. Severe alcoholic hepatitis may persist for several months despite abstinence and, if any question of continued activity exists, a liver biopsy should be repeated (260). In cases of urgent or emergent surgery

on patients with alcohol dependence, administration of tapered doses of *benzodiazepine* is appropriate as prophylaxis against alcohol withdrawal.

Cirrhosis

Cirrhosis is an irreversible liver lesion characterized histologically by parenchymal necrosis, nodular degeneration, fibrosis, and a disorganization of hepatic lobular architecture. The most serious complication of cirrhosis is portal venous hypertension, which ultimately leads to bleeding from esophageal varices, ascites, and hepatic encephalopathy. Conventional liver biochemical test results correlate poorly with the degree of liver impairment in patients with cirrhosis. Hepatic dysfunction, however, may be somewhat quantitated by low albumin levels and prolonged prothrombin times.

Surgical risk is clearly increased in patients with advanced liver disease, although it is substantially greater in emergency surgery than in elective surgery.

Perioperative mortality correlates with the severity of cirrhosis and can be estimated through the use of the Child's classification (see Table 20.20). In patients with Child's class A cirrhosis, surgery can usually be performed without significant risk, whereas in patients with Child's class B or C, surgery poses a major risk and requires careful preoperative consideration.

Preoperative preparation should include the following measures: (i) optimizing nutritional status by enteral and parenteral nutrition and supplementation with B₁, (ii) correcting coagulopathy with administration of FFP or cryoprecipitate or both, (iii) minimizing pre-existing encephalopathy, (iv) preventing sepsis from spontaneous bacterial peritonitis by

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administering prophylactic antibiotic therapy, and (v) optimizing renal function and carefully correcting electrolyte abnormalities (261). Meticulous preoperative preparation focused on correcting abnormalities associated with advanced liver disease may improve surgical outcomes (262).

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21

Gynecologic Endoscopy

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- Positioning of the insufflation needle, the primary trocar, and the cannula are best accomplished with the patient in an unaltered horizontal position.
- Proper patient selection is critical for laparoscopic management of ovarian cysts because of concerns about an adverse effect on prognosis with malignant tumors.
- Laparoscopic myomectomy often requires laparoscopic suturing; thus, more technical skills are needed than with many other endoscopic procedures.
- Dehiscence and hernia risk appear to significantly increase when the fascial incision is larger than 10 mm in diameter.
- Patients recovering from laparoscopic surgery usually feel better every day. Pain diminishes, gastrointestinal function improves rapidly, and fever is extremely unusual. Therefore, if a patient's condition is not improving, possible complications of anesthesia or surgery should be considered.

The incidence of unintended electrosurgical activation injuries can be reduced if the surgeon is always in direct control of electrode activation and if all electrosurgical hand instruments are removed from the peritoneal cavity when not in use.

Endoscopy is a procedure that uses a narrow telescope to view the interior of a viscus or preformed space. Although the first medical endoscopic procedures were performed more than 100 years ago, the potential of this method has only recently been realized. Endoscopes are currently used to perform a variety of operations. **In gynecology, endoscopes are used most often to diagnose conditions by direct visualization of the peritoneal cavity (laparoscopy) or the inside of the uterus (hysteroscopy).**

When used appropriately, endoscopic surgery offers the benefits of reduced pain, improved cosmesis, lower cost, and faster recovery. The indications for endoscopic

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surgery are outlined here and described in more detail in the appropriate chapters. The technology, potential uses, and complications of laparoscopy and hysteroscopy are summarized here.

Laparoscopy

The past three decades have witnessed rapid progress and technologic advances in laparoscopy (1,2,3,4,5,6,7,8,9,10,11,12). Operative laparoscopy was developed in the 1970s, and in the early 1980s, laparoscopy was first used to direct the application of electrical or laser energy for the treatment of advanced stages of endometriosis (6,7). The use of high-resolution, lightweight video cameras in operative laparoscopy has made it easier to view the pelvis during the performance of complex procedures (7,8,9,10). Subsequently, many other procedures that previously were performed using traditional techniques, such as hysterectomy, became feasible with the laparoscope (11). However, the endoscopic approach may have drawbacks in some patients. Although some laparoscopic procedures appear to reduce the cost and morbidity associated with surgery, others have not been shown to be effective replacements for more traditional operations. The techniques and indications for operative endoscopy are evolving.

Diagnostic Laparoscopy

The objective lens of a laparoscope can be positioned to allow wide-angle or magnified views of the peritoneal cavity. The clarity and illumination of the optics allow a better appreciation of fine detail than is possible with the naked eye. Laparoscopy is the standard method for the diagnosis of endometriosis and adhesions because no other imaging technique provides the same degree of sensitivity and specificity.

There are limitations to laparoscopy, however. The view of the operative field may be restricted, and if tissue or fluid becomes attached to the lens, vision may be obscured. Also, soft tissues, intramural myomas, or the inside of a hollow viscus cannot be palpated. For assessment of these tissues, an imaging modality, such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) scans, is superior. **Because of its ability to view soft tissue, ultrasonography is more accurate than laparoscopy for the evaluation of the inside of adnexal masses. The intraluminal contour of the uterus can be shown only by hysteroscopy or contrast imaging. Ultrasonography, in combination with serum assays of β -human chorionic gonadotropin (β -hCG) and progesterone, can be used to diagnose ectopic pregnancy, usually allowing medical therapy to be given without laparoscopic confirmation** (12). As a result of

the advances in blood tests and imaging technology, laparoscopy is more often used to confirm a clinical impression than for initial diagnosis.

Laparoscopy may disclose abnormalities that are not necessarily related to the patient's problem. Although endometriosis, adhesions, leiomyomas, and small cysts in the ovaries are common, they are frequently asymptomatic. Thus, **diagnostic laparoscopy must be performed prudently**, interpreting findings in the context of the clinical problem and other diagnoses.

Therapeutic (Operative) Laparoscopy

The role of laparoscopy in the operative management of gynecologic conditions is evolving. Many procedures previously performed as traditional abdominal and vaginal operations are feasible with laparoscopy. Operative laparoscopy has the benefit of shorter hospital stays, less postoperative pain, and faster return to normal activity. In addition to

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the benefits of endoscopic procedures in general, adhesions are less likely to form with laparoscopic surgery than with laparotomy. Because sponges are not used, the amount of direct peritoneal trauma is reduced substantially, and contamination of the peritoneal cavity is minimized. The lack of exposure to air allows the peritoneal surface to remain more moist and, therefore, less susceptible to injury and adhesion formation.

Despite these advantages, there are potential limitations: exposure of the operative field can be reduced, small instruments are required and can be used only through fixed ports, the ability to manipulate the pelvic viscera is limited, and the caliber of the suture required may be larger than otherwise desired. In many cases, the cost of hospitalization increases, despite a shortened stay, because of prolonged operating room time and the use of more expensive surgical equipment and supplies. Efficacy may be reduced if a surgeon cannot adequately replicate the abdominal operation. In some patients, there is an increased risk of complications, which can be attributed to the innate limitations of laparoscopy, the level of surgical expertise, or both. With an adequate combination of ability, training, and experience, however, operative time and complications are comparable to those of traditional abdominal surgery.

Tubal Surgery

Sterilization

Laparoscopic sterilization has been extensively used since the late 1960s and can be performed under general anesthesia. The fallopian tubes can be occluded by suture, clips, or Silastic rings, but electrosurgical desiccation with bipolar energy is the technique used most often (see Chapter 10). With operative laparoscopy, only one incision is required. Otherwise, a second port is needed for the introduction of the occluding instrument. Patients remain in the hospital for several hours, even when general anesthesia is used. Postoperative pain is usually minor and related to the effects of the anesthesia, gas that remains in the peritoneal cavity (shoulder pain, dyspnea), and in the case of occlusive devices, pain at the surgical site. These effects normally disappear within a few days. The failure rate is about 5.4 per 1,000 woman-years (13,14).

Ectopic Gestation

Medical therapy with *methotrexate* is considered first-line therapy for tubal pregnancies that meet the following criteria: no cardiac activity, tubal mass smaller than 5 cm confirmed

by ultrasonography, and β -hCG level less than 1,000 (15). **Ectopic gestation can be managed by using laparoscopy to perform the same procedures done with laparotomy, including salpingotomy, salpingectomy, and segmental resection of a portion of the oviduct** (see Chapter 18) (16). Salpingotomy is performed with scissors, a laser, or an electrosurgical electrode after carefully injecting the mesosalpinx with a dilute *vasopressin*-containing solution (20 units per 100 mL of normal saline). For salpingectomy, the vascular pedicles are usually secured with electrosurgical desiccation, ligatures, clips, or a combination thereof. Tissue is removed from the peritoneal cavity through one of the ports of the laparoscope.

When salpingotomy is performed, regardless of the route, there is about a 5% chance that trophoblastic tissue remains. In such instances, medical treatment with *methotrexate* is considered appropriate (see Chapter 18). Consequently, β -hCG levels should be measured weekly until there is confidence that complete excision has occurred (17,18).

Ovarian Surgery

Ovarian Masses

Laparoscopic removal of selected ovarian masses is a well-established procedure (19,20). However, proper patient selection is critical for laparoscopic management of tumors because of its adverse effect on prognosis with malignant tumors (21). Preoperative ultrasonography is mandatory. Sonolucent lesions with thin

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walls and no solid components are at very low risk for malignancy and, therefore, are suitable for laparoscopic removal. For postmenopausal women, the measurement of CA125 levels is useful in identifying candidates for laparoscopic management (22,23). Lesions with ultrasonographic findings suggestive of mature teratoma (dermoid), endometrioma, or hemorrhagic cyst with acute pain may also be suitable for endoscopic management (24).

Ovarian tumors should be assessed by frozen histologic section, and any malignancy should be managed expeditiously by laparotomy (20,23).

The technique for performing laparoscopy for oophorectomy and cystectomy is similar to that used for laparotomy (17). For cystectomy, scissors are used to incise the ovarian capsule, and blunt dissection or aquadissection are used to separate the cyst from the ovary. If oophorectomy is performed, the vascular pedicles are ligated with sutures, clips, linear cutting staplers, electrosurgical desiccation, or a combination thereof. The ureter should be identified and should be clear of the pedicle to be ligated. Cysts that appear to be benign may be drained before extraction through either a laparoscopic cannula or, rarely, a posterior colpotomy. If there is concern about the impact of spilled cyst contents, the specimen should be removed in a retrieval bag inserted into the peritoneal cavity.

Although in the past the ovary has routinely been closed after cystectomy, this practice may be unnecessary and could contribute to the formation of adhesions (25). However, complete disruption of the ovarian cortex after removal of large cysts may make closure necessary, in which case the edges of the ovarian incision can be sutured.

Other Ovarian Surgery

Ovarian torsion, previously treated by laparotomy and oophorectomy, often can be managed laparoscopically (26,27). Even if there is apparent necrosis, the adnexa can be untwisted, usually with preservation of normal ovarian function (28). Performing a cystectomy at the same time the ovary is untwisted greatly reduces the likelihood that ovarian function will

be maintained. Rarely is adnexectomy indicated.

Polycystic ovarian syndrome can be treated laparoscopically using electrosurgery and laser vaporization to perform ovarian drilling. This procedure reduces stromal tissue and may lead to a temporary return to normal ovulation (29,30,31). Although such procedures have been shown to be successful, postoperative adhesions form in 15% to 20% of patients, which underscores the need to first exhaust medical treatment (32,33).

Uterine Surgery

Myomectomy

Laparoscopic myomectomy, although feasible, is difficult to perform. Its efficacy is yet to be established, especially as it relates to the treatment of infertility and menorrhagia (34,35). Laparoscopic myomectomy often requires laparoscopic suturing and, thus, requires more technical skills than many other endoscopic procedures.

Unless the myoma involves the endometrial cavity, it is unlikely to contribute to heavy menstrual bleeding. Leiomyomas that cause pressure are often large and may be located in or near vital vascular structures. Myomectomy should be performed only when indicated (as opposed to expectant or medical management, which may be appropriate for some women with leiomyomas), and laparotomy should be used if there are technical limitations (36). **Patients who have pedunculated or subserosal leiomyomas that cause bothersome discomfort or pain in association with torsion are candidates for laparoscopic excision** (17,37).

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Hysterectomy

For women who require hysterectomy, the appropriate route of surgery is determined by anatomical considerations, the type of pathology expected, patient preference, and physician experience and training. Laparoscopic hysterectomy offers no advantage for women in whom vaginal hysterectomy is possible because the endoscopic approach is more expensive and has a higher risk for postoperative morbidity (38,39). However, 75% of the approximately 600,000 hysterectomies performed in the United States are abdominal hysterectomies. Indications for choosing an abdominal approach are known or suspected pelvic adhesions or endometriosis, leiomyomata, the presence of adnexal pathology, the need for mandatory removal of the adnexa, or the absence of pelvic relaxation. In many patients, hysterectomy can be performed under laparoscopic direction.

Laparoscopic hysterectomy encompasses a variety of procedures, including the facilitation of vaginal hysterectomy with variable extents of endoscopic dissection, supracervical hysterectomy by dissection, amputation and mechanical removal of the fundus, and the removal of the entire uterus with the assistance of the laparoscope (40). The procedure is performed with scissors, sutures, electricity, clips, and in some instances, linear cutting and stapling devices to dissect or ligate pedicles.

There is a slightly higher risk of complications with laparoscopic hysterectomy, and operating times may be longer and procedures more costly than with abdominal hysterectomy. As experience is gained with laparoscopic hysterectomy, these outcomes approach those of abdominal hysterectomy. When reusable instruments are employed, however, laparoscopic hysterectomy is less costly than abdominal hysterectomy (41). Most studies show less postoperative pain, shorter hospital stays, and faster postoperative recovery with laparoscopic hysterectomy than with abdominal hysterectomy (42).

One study found pain scores and quality-of-life measures, including sexual activity and physical and mental functioning, were significantly better for women who underwent laparoscopic versus abdominal hysterectomy (42). These differences were present at 6 weeks following surgery and remained at the 12-month follow-up visit.

Infertility Operations

Laparoscopic treatment of infertility includes operations used to reconstruct the normal anatomic relationships altered by an inflammatory process such as fimbrioplasty, adhesiolysis, and salpingostomy for distal obstruction (43). Fimbrioplasty is distinguished from salpingostomy because it is performed in the absence of pre-existing complete distal obstruction. Endometriosis associated with adnexal distortion can be treated by laparoscopic adhesiolysis. There is no known additional benefit of laparoscopic (or medical) treatment of coexistent active endometriosis. Laparoscopy has been superseded by ultrasound for the retrieval of oocytes for *in vitro* fertilization but is still used for procedures in which gametes (gamete intrafallopian transfer) or zygotes (zygote intrafallopian transfer) are placed into the fallopian tube.

Adhesiolysis may be accomplished by blunt or sharp dissection with scissors, laser, ultrasonic shears, or electrosurgical electrode. These instruments are usually passed through an ancillary port; when laser energy is used, the channel of the operating laparoscope may be used for this purpose. Although there has been controversy regarding the most appropriate modality for adhesiolysis, these methods are probably equally effective in appropriately trained hands.

Laparoscopic operations for the treatment of mechanical infertility are probably equally effective to similar procedures performed by laparotomy. In patients with extensive adhesions, however, the effectiveness of all procedures is limited. Assisted reproductive technologies such as *in vitro* fertilization and embryo transfer are necessary in these situations (see Chapter 30) (17,44).

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Endometriosis

The laparoscopic management of endometriomas parallels that of adnexal masses, although the ultrasonographic complexity of endometriomas sometimes makes it difficult to distinguish them preoperatively from a neoplasm. The close attachment of the endometrioma to the ovarian cortex and stroma may make it difficult to find surgical dissection planes, and incomplete removal increases the risk of recurrence. There is a tendency either to compromise the function of the remaining ovary by attempting complete removal or to leave part of the endometrioma in place. Therefore, for women who want to retain their fertility, electrosurgical or laser ablative techniques may be used to treat endometriotic tissue that is adherent to the remaining ovary.

Multifocal endometriosis may be treated by mechanical excision or ablation, the latter using coagulation or vaporization with either electrical or laser energy. With proper use, each energy source creates about the same amount of thermal injury (45,46). Endometriosis frequently is deeper than appreciated initially, making excisional techniques valuable in many instances (17,44).

Pelvic Floor Disorders

Laparoscopy can be used to guide procedures to treat pelvic support defects, including culdoplasty, enterocele repair, vaginal vault suspension, paravaginal repair,

and retropubic cystourethropey for urinary stress incontinence. Although these conditions can be treated vaginally, the laparoscopic approach may offer benefits, particularly with retropubic urethropey. There is some evidence that the laparoscopic approach is effective when compared with the traditional methods (47,48). Using the same surgical principles applied during traditional pelvic floor repair, laparoscopy promises better access to key anatomical landmarks and potentially more accurate suture placement (49). Whereas apical and anterior compartment defects can be successfully corrected via laparoscopy, posterior and perineal defects are still best visualized and repaired using vaginal techniques. The laparoscopic treatment of enterocele and vault prolapse may be useful in patients who require abdominal approaches after failure of a previous vaginal procedure. Because of the anatomical proximity of the pelvic ureter to the uterosacral ligament and anterolateral vagina, bilateral ureteral patency should be confirmed cystoscopically after laparoscopic vaginal vault suspension, enterocele repair, culdoplasty, cystourethropey, or paravaginal repair.

Gynecologic Malignancies

The role of laparoscopy in the management of gynecologic malignancy has not been clearly established (50,51,52). A study performed by the Gynecology Oncology Group showed that laparoscopic management of presumed stage I endometrial cancer was feasible (53), whereas another study found that women with endometrial cancer and other comorbidities had fewer complications with laparoscopically assisted vaginal hysterectomy than with laparotomy (54). The potential for laparoscopic lymphadenectomy has fostered a resurgence of interest in vaginal radical hysterectomy for stage I carcinoma of the cervix. Laparoscopy is also being investigated for the staging of early ovarian malignancy and for second-look surgery.

Patient Preparation and Communication

The rationale, alternatives, risks, and potential benefits of the selected approach should be explained to the prospective patient. She should know the likely outcome of expectant management if the procedure was not performed.

The expectations and risks of diagnostic laparoscopy, as well as those of any other procedures that may be needed, must be explained. It may be helpful to compare risks and recovery with the same procedure performed via abdominal surgery. The risks of laparoscopy include those associated with anesthesia, infection, bleeding, and injury to the

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abdominal and pelvic viscera. The possibility of conversion to laparotomy if a complication should occur or if the procedure cannot be completed via laparoscopic surgery should also be discussed. Infection is uncommon with laparoscopic surgery. For procedures involving extensive dissection, there is a higher risk for visceral injury. The potential for these risks should be clearly presented. The patient should be given realistic expectations regarding postoperative disability. **Because pain and visceral dysfunction normally continue to improve after uncomplicated laparoscopy, the patient should be instructed to communicate immediately any regression in her recovery.** After diagnostic or brief operative procedures, patients can be discharged on the day of surgery and usually require 24 to 72 hours off work or school. If extensive dissection—a major surgical procedure performed laparoscopically—is necessary, or if the surgery lasts longer than 2 hours, hospital admission may be necessary, and the period of disability may be as long as 10 to 14 days.

If the procedure may involve the colon, mechanical bowel preparation should

be performed to help improve visualization and minimize the likelihood of fecal spillage if the colon is entered. The patient should arrange for a friend or family member to be present to discuss the results of the procedure with the physician and to drive her home if she is discharged the same day. Mild analgesia often is necessary.

Equipment and Technique

To facilitate the discussion of laparoscopic equipment, supplies, and techniques, it is useful to divide procedures into "core competencies," which are as follows:

- Patient positioning
- Operating room organization
- Peritoneal access
- Visualization
- Manipulation of tissue and fluid
- Cutting, hemostasis, and tissue fastening
- Tissue extraction
- Incision management

Patient Positioning

Proper positioning of the patient is essential for patient safety, comfort of the operator, and optimal visualization of the pelvic organs. Laparoscopy is performed on an operating table that can be tipped to create a steep, head-down (Trendelenburg) position that allows the bowel to move out of the pelvis after the first trocar has been placed. The footrest can be dropped to allow access to the perineum. The patient is placed in the low lithotomy position, with the legs supported in stirrups and the buttocks protruding slightly from the lower edge of the table (Fig. 21.1). The thighs are usually kept in the neutral position to preserve the sacroiliac angle, reducing the tendency of bowel to slide into the peritoneal cavity. **The feet should rest flat, and the lateral aspect of the knee should be protected with padding or a special stirrup to avoid peroneal nerve injury.** The knees should be kept in at least slight flexion to minimize stretching of the sciatic nerve and to provide more stability in the Trendelenburg position. **The arms are positioned at the patient's side by adduction and pronation to allow freedom of movement for the surgeon and to lower the risk for brachial plexus injury** (Fig. 21.2). Care must be exercised to protect the patient's fingers and hands from injury when the foot of the table is

raised or lowered. After the patient is properly positioned, the bladder should be emptied with

a catheter and a uterine manipulator attached to the cervix.

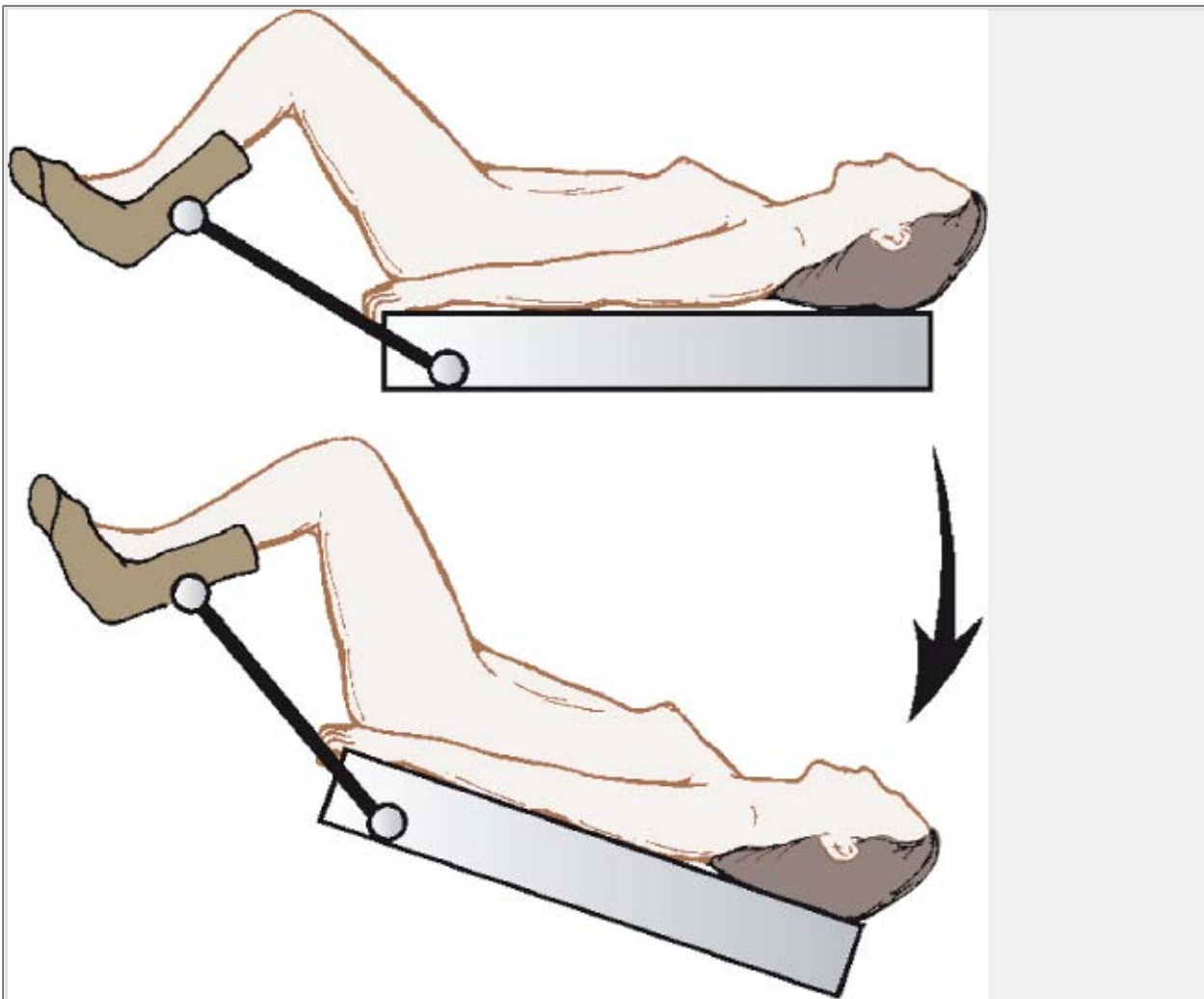
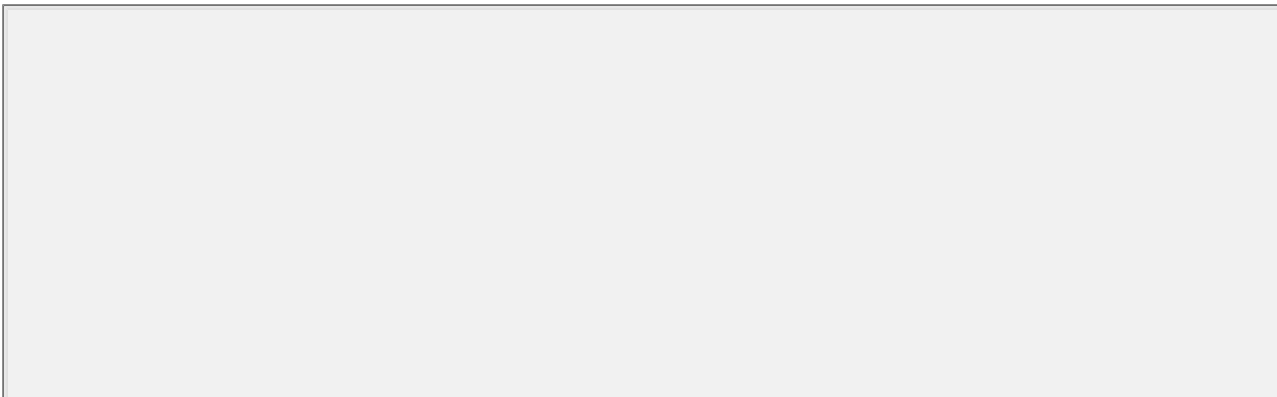


Figure 21.1 Patient positioning: the low lithotomy position. The patient's buttocks are positioned so that the perineum is at the edge of the table. The legs are well supported with stirrups, with the thighs in slight flexion. Too much flexion may impede the manipulation of laparoscopic instruments while in the Trendelenburg (head-down) position.

Operating Room Organization

The arrangement of instruments and equipment is important for safety and efficiency. The orientation depends on the operation, the instruments used, and whether the surgeon is right- or left-handed. An orientation for a right-handed operator is shown in Figure 21.2.



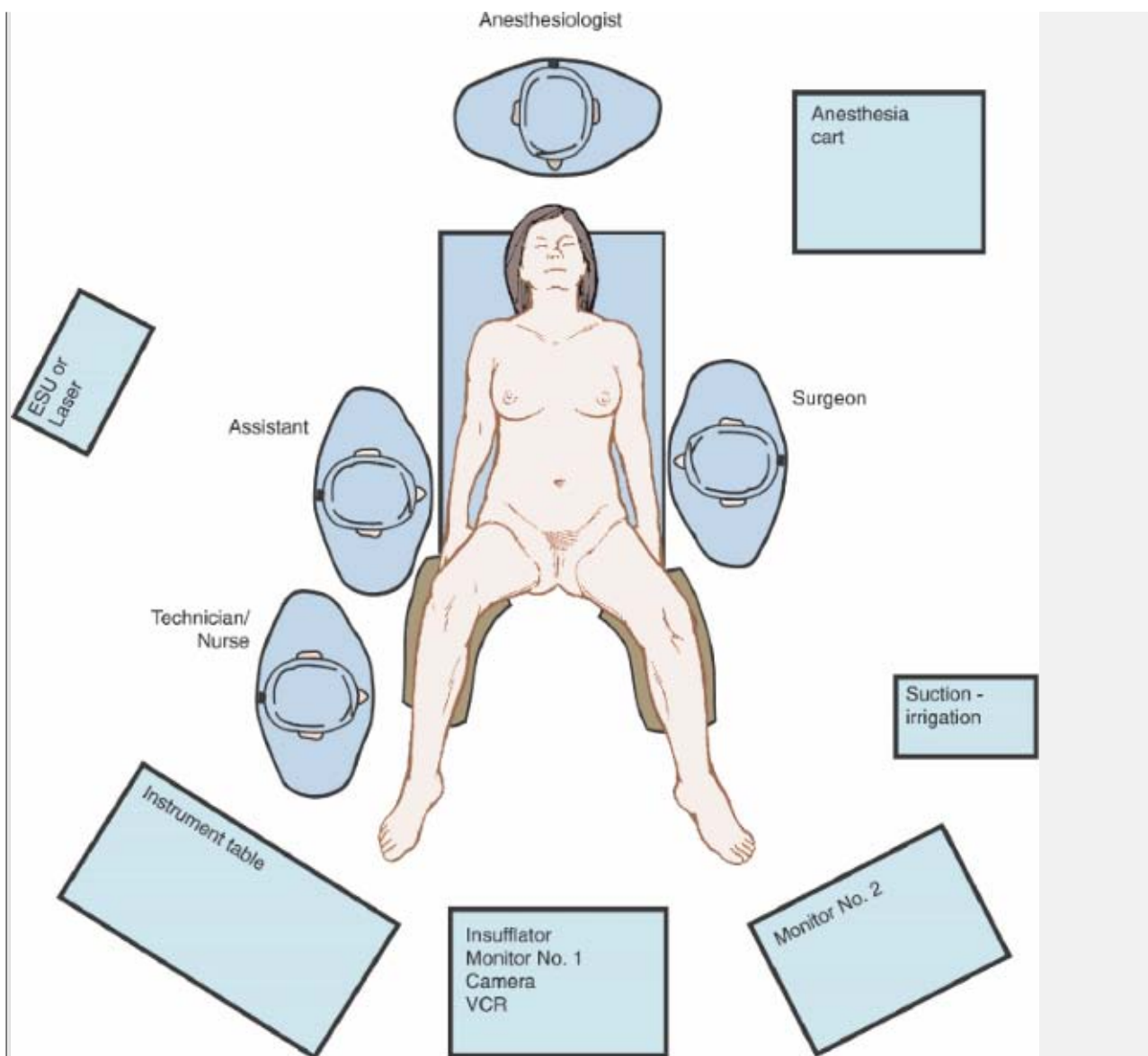


Figure 21.2 Operating room organization. The patient's arms are at the sides. The right-handed surgeon stands on the patient's left. Instruments and equipment are distributed around the patient within view of the surgeon. For pelvic surgery, the monitor should be located between the patient's legs.

For pelvic surgery, the monitor may be placed at the foot of the table within the angle formed by the patient's legs. If a second monitor is used, one may be positioned at each foot of the patient.

The surgeon usually stands by the patient's left side, at an angle facing the patient's contralateral foot. The nurse or technician and instrument table are positioned near the foot of the operating table to avoid obscuring the video monitor. The insufflator may be placed on the patient's right side, in front of the surgeon, to allow continuous monitoring of the inflation rate and intra-abdominal pressure. The electro-surgical generator may also be positioned on the patient's right side to permit visualization of the power output. When a laser is used through a second puncture site, it may also be placed to the patient's right.

When the laser is passed through the channel of an operating laparoscope, however, it may be situated on the patient's left side, beside the surgeon.

Peritoneal Access

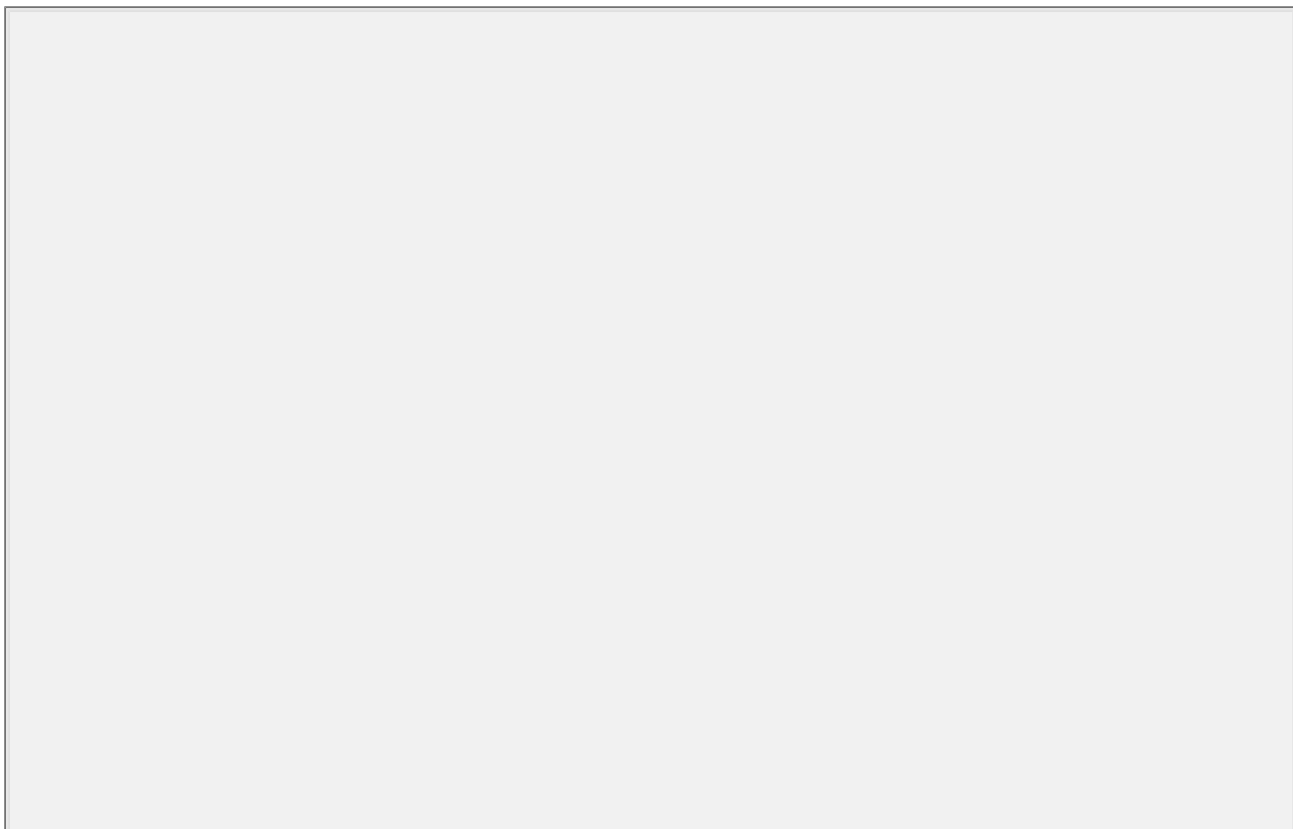
Before inserting the laparoscope, a cannula or port must be positioned in the abdominal wall to establish access to the peritoneal cavity. **The closed technique is a blind approach in which the cannula is introduced with a sharp trocar used to penetrate the abdominal layers. In open laparoscopy, entry into the peritoneal cavity is achieved with minilaparotomy using either a transverse subumbilical or midline infraumbilical incision down to the rectus fascia, to which the cannula is fixed into position with sutures or other suitable techniques.** Gynecologists have generally favored a closed technique, preinflating the peritoneal cavity with CO₂ through a hollow insufflation needle. In either case, additional cannulas are subsequently inserted by sharp trocars under direct vision to allow the use of laparoscopic hand instruments such as scissors, probes, and other manipulating devices.

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Insertion of the insufflation needle and primary cannula is aided by an understanding of the normal underlying anatomy, especially the location of the larger retroperitoneal vessels (Fig. 21.3). A "safety zone" exists inferior to the sacral promontory in the area bounded cephalad by the bifurcation of the aorta, posteriorly by the sacrum, and laterally by the iliac vessels (49). In women placed in the Trendelenburg position, the great vessels are situated more cephalad and anterior, making them more vulnerable to injury unless appropriate adjustments are made in the angle of insertion (Fig. 21.4) (55). Therefore, positioning of the insufflation needle, the primary trocar,

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and the cannula are best accomplished with the patient in an unaltered horizontal position. This approach also facilitates the evaluation of the upper abdomen, which is limited if the intraperitoneal contents are shifted cephalad by the head-down position.



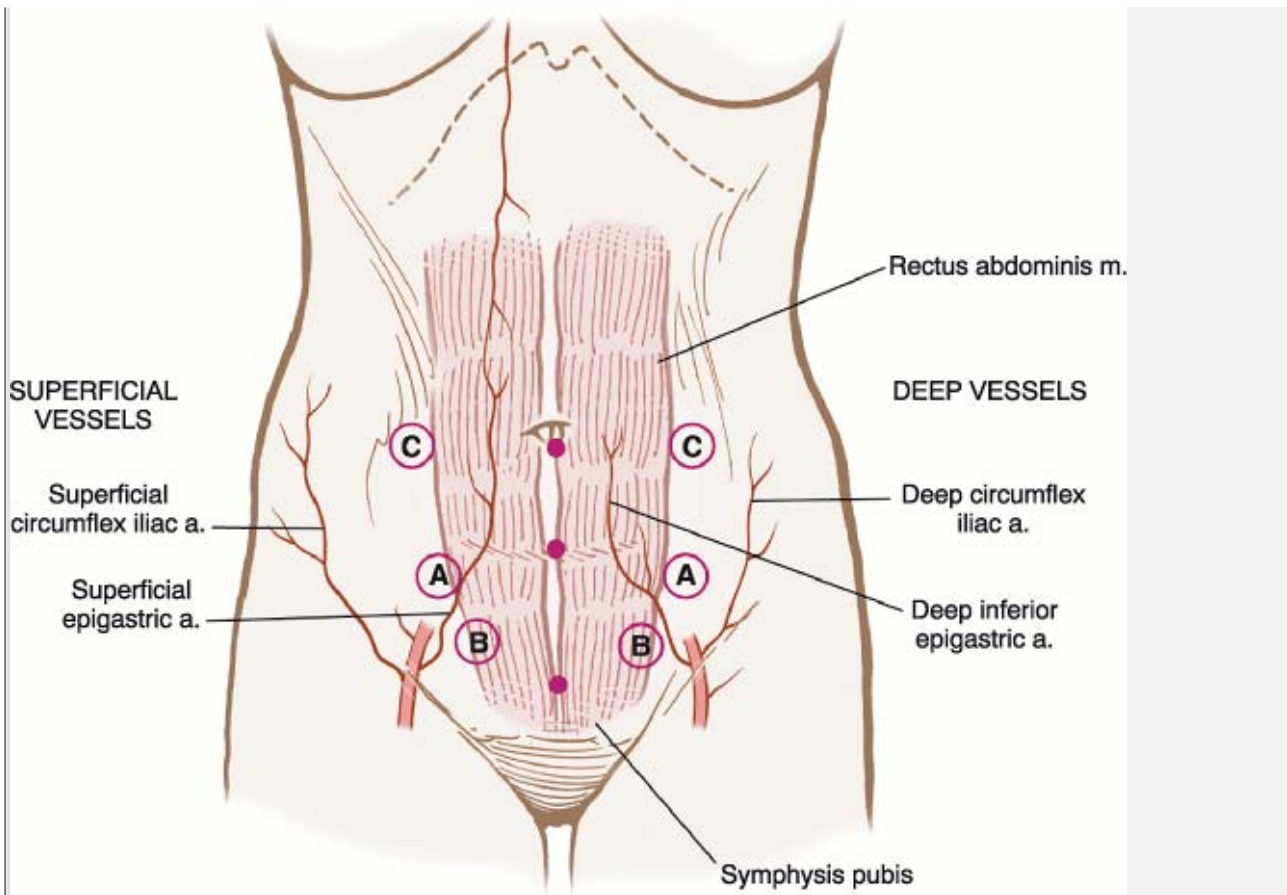


Figure 21.3 Vascular anatomy of the anterior abdominal wall. Location of the vessels that can be traumatized when inserting trocars into the anterior abdominal wall.

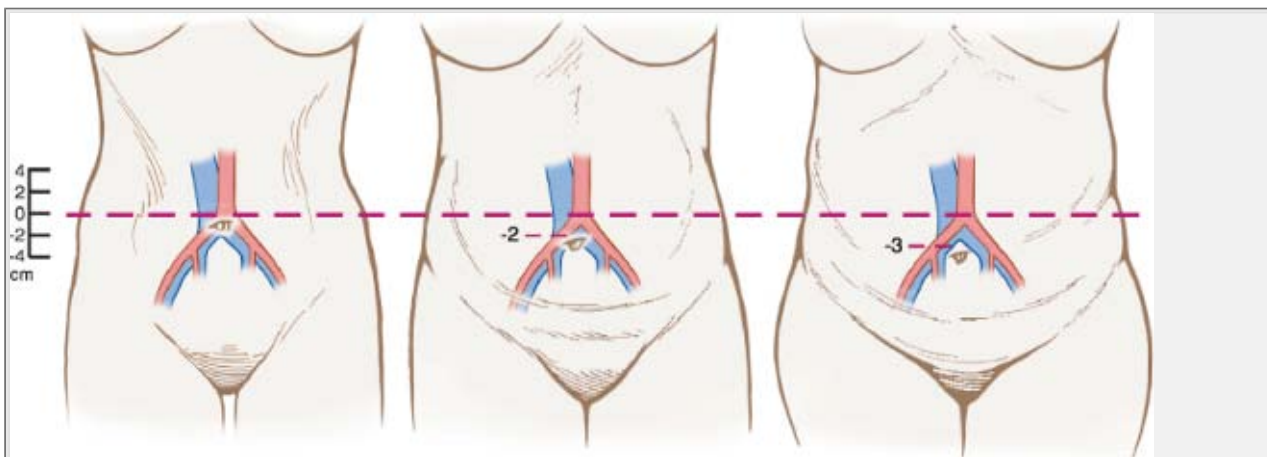


Figure 21.4 Vascular anatomy. Location of the great vessels and their changing relationship to the umbilicus with increasing patient weight (*from left to right*).

Insufflation Needles

Virtually all insufflation needles are modifications of the hollow needle designed by Verres (Fig. 21.5). In cases uncomplicated by previous pelvic surgery, the preferred site for insertion is the base of the umbilicus, where the abdominal wall is the thinnest and usually avascular.

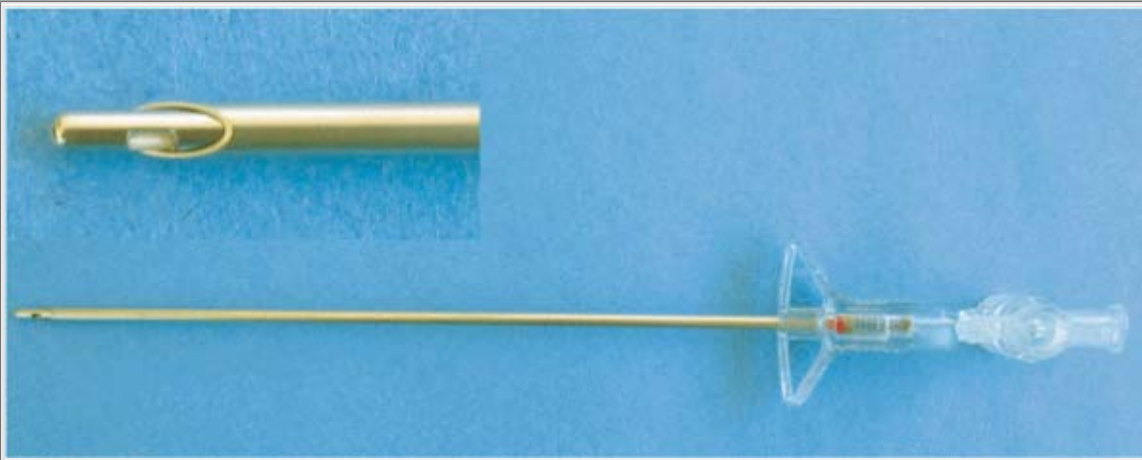


Figure 21.5 Insufflation needle. When pressed against tissue such as fascia or peritoneum, the spring-loaded blunt obturator (*inset*) is pushed back into the hollow needle, revealing its sharpened end. When the needle enters the peritoneal cavity, the obturator springs back into position, protecting the intraabdominal contents from injury. The handle of the hollow needle allows the attachment of a syringe or tubing for insufflation of the distention gas.

A midline infraumbilical incision adequate for the needle is made at the base of the umbilicus with a small scalpel, and the abdominal wall is maximally lifted, either manually or with instruments. Elevation is accomplished manually by grasping on either side lateral to the umbilicus or midway between the umbilicus and mons pubis. Instrumentally, elevation can be achieved by affixing towel clips to the abdominal wall on either side lateral to the umbilicus or opposite one another within the edge of the umbilical incision itself (56).

Safe insertion of the insufflation needle mandates that the instrument be maintained in a midline, sagittal plane while the operator directs the tip between the iliac vessels, anterior to the sacrum but inferior to the bifurcation of the aorta and the proximal aspect of the vena cava. Because the sacral promontory is commonly covered in part by the left common iliac vein, vascular injury may still occur in the midline below the bifurcation (57).

To reduce the risk of retroperitoneal vascular injury while minimizing the chance of inadvertent preperitoneal insufflation, in women of average weight, **the insufflation needle is directed to the patient's spine at a 45-degree angle.** In heavy to obese individuals, this angle may be increased incrementally to nearly 90 degrees, accounting for the increasing thickness of the abdominal wall and the tendency of the umbilicus to gravitate caudad with increasing abdominal girth (58). The needle's shaft is held by the tips of the fingers and steadily but purposefully guided into position only far enough to allow the tip's entry into the peritoneal cavity. The tactile and visual feedback created when the needle passes through the facial and peritoneal layers of the abdominal wall may

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provide guidance and help prevent overaggressive insertion attempts. This proprioceptive feedback is less apparent with disposable needles than with the classic Verres needle. With the former, the surgeon must listen to the "clicks" as the needle obturator retracts when it passes through the rectus fascia and the peritoneum. The needle should never be forced. Regardless of technique, the underlying retroperitoneal vessels are protected ultimately by limiting the depth of insertion of the insufflation needle and umbilical cannula.

In instances in which known or suspected intra-abdominal adhesions surround the umbilicus, alternative sites should be used for insufflation needle insertion. These sites include the left upper quadrant, most often at the left costal margin, the pouch of Douglas, and the fundus of the uterus (Fig. 21.6). The left upper quadrant is preferred if hepatosplenomegaly is not present and the patient has not previously had surgery in this area. In such patients, the stomach must be decompressed with a nasogastric or orogastric tube before the needle is inserted (59).

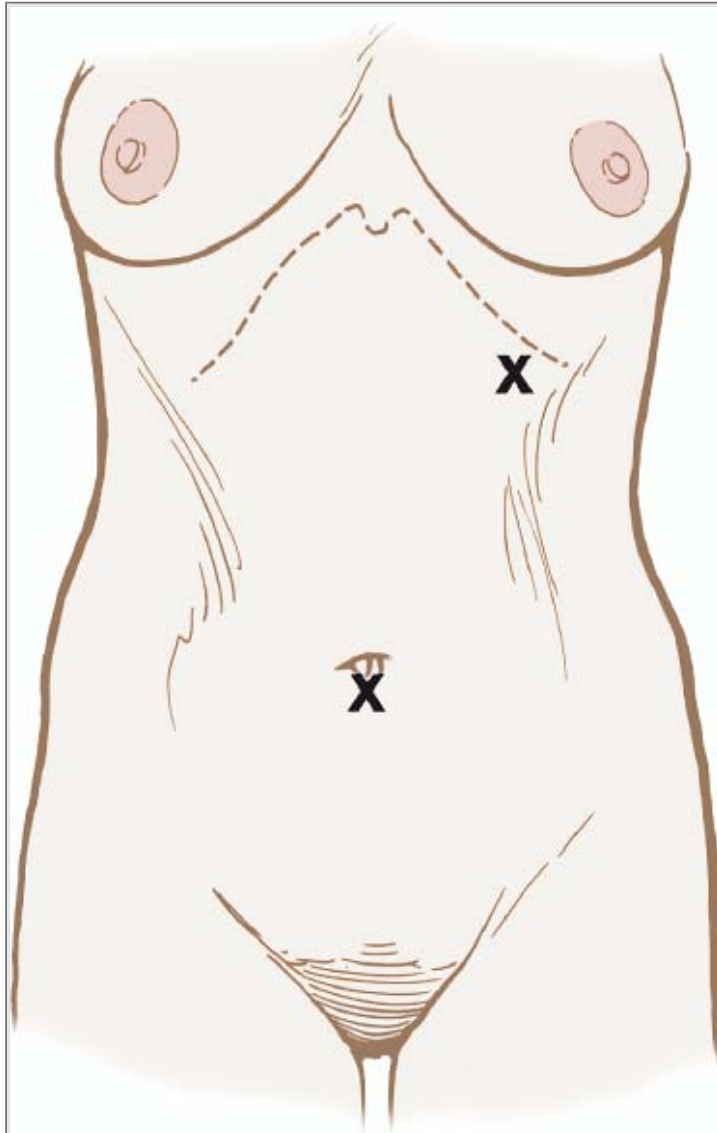


Figure 21.6 Insufflation needle and cannula insertion sites. In most instances, both the insufflation needle, if used, and the primary cannula are inserted through the umbilicus. When subumbilical adhesions are known or suspected, the insufflation needle may be placed through the pouch of Douglas or in the left upper quadrant after evacuation of the gastric contents with an orogastric tube.

Before insufflation, the operator should try to detect whether the insufflation needle has been malpositioned in the omentum, mesentery, blood vessels, or hollow organs such as the stomach or bowel. Using a syringe attached to the

insufflation needle, blood or gastrointestinal contents may be aspirated. To facilitate this examination, a small amount of saline may be injected into the syringe. If the needle is appropriately positioned, negative intra-abdominal pressure is created by lifting the abdominal wall. This negative pressure may be demonstrated by aspiration of a drop of saline placed over the open, proximal end of the needle or, preferably, by using the digital pressure gauge on the insufflator.

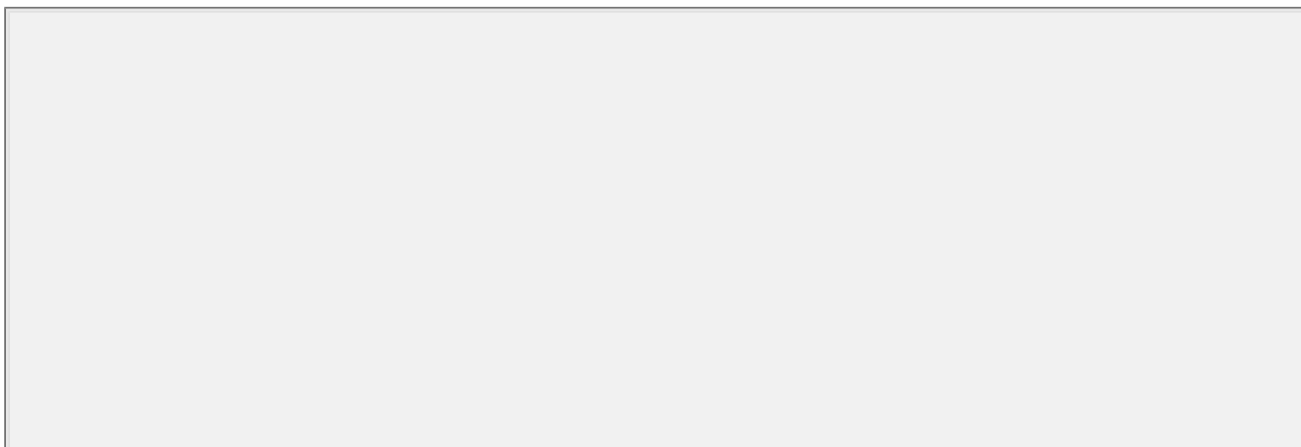
- **Additional signs of proper placement may be sought after starting insufflation. The intra-abdominal pressure reading should be low, reflecting only systemic resistance to the flow of CO₂.** Consequently, there should be little deviation from a baseline

measurement, generally less than 10 mm Hg. The pressure varies with respiration and is slightly higher in obese patients. The earliest reassuring sign is the loss of liver "dullness" over the lateral aspect of the right costal margin. However, this sign may be absent if there are dense adhesions in the area, usually the result of previous surgery. Symmetric distention is unlikely to occur when the needle is positioned extraperitoneally. Proper positioning can also be shown by lightly compressing the xiphoid process, which increases the pressure measured by the insufflator.

- **The amount of gas transmitted into the peritoneal cavity should depend on the measured intraperitoneal pressure, not the volume of gas inflated.** Intraperitoneal volume capacity varies significantly between individuals. Many surgeons prefer to insufflate to 25 mm Hg for positioning of the cannulas. This level usually provides extra volume and enough counterpressure against the peritoneum, facilitating trocar introduction and potentially reducing the chance of bowel or posterior abdominal wall and vessel trauma. After placement of the cannulas, the pressure should be dropped to 10 to 12 mm Hg, which reduces the risk of subcutaneous insufflation leading to crepitus and essentially eliminates hypercarbia or decreased venous return of blood to the heart (59,60,61).

Laparoscopic Cannulas

Laparoscopic cannulas allow the insertion of laparoscopic instruments into the peritoneal cavity while maintaining the pressure created by the distending gas (Figs. 21.7 and 21.8). Cannulas are hollow tubes with a valve or sealing mechanism at or near the proximal end. The cannula may be fitted with a Luer-type port that allows attachment to tubing connected with the CO₂ insufflator. Larger-diameter cannulas (8–12 mm) may be fitted with adapters or specialized valves that allow the insertion of smaller-diameter instruments without loss of intraperitoneal pressure.



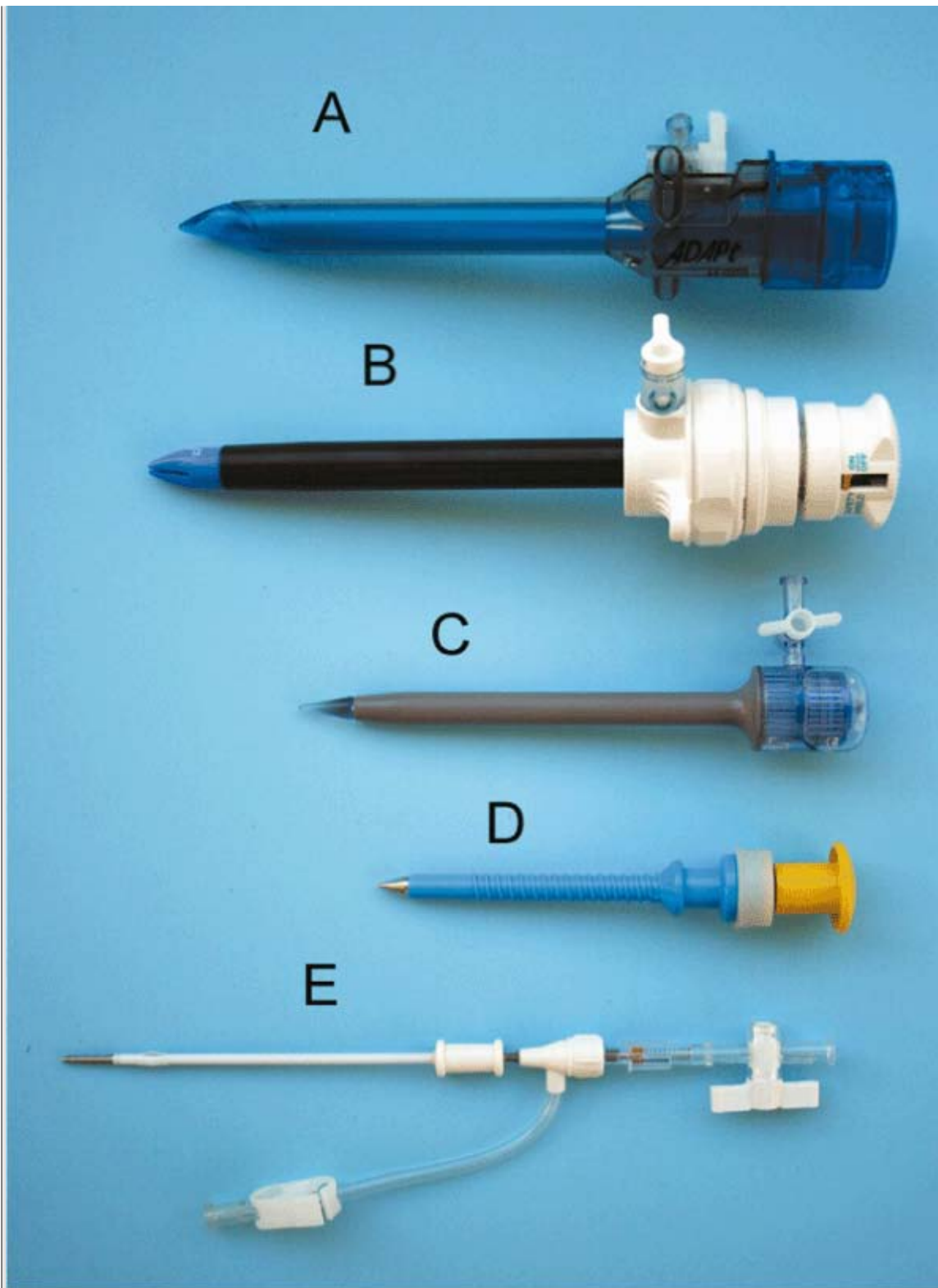


Figure 21.7 Disposable access systems. These instruments are designed for single use. A 12-mm internal diameter blunt access system is shown in **A**. The next device (**B**) also has a 12 mm internal diameter, but has a deployable blade that is used to cut through the abdominal wall. A smaller diameter blunt conical device is shown in **C** while a sharp conical access system is presented in **D**. Both **C** and **D** have a 5 mm in inside diameter. A narrow, 2.7-mm diameter cannula is shown in **E**. The trocar for this system is a long insufflation needle with a spring deployable obturator.

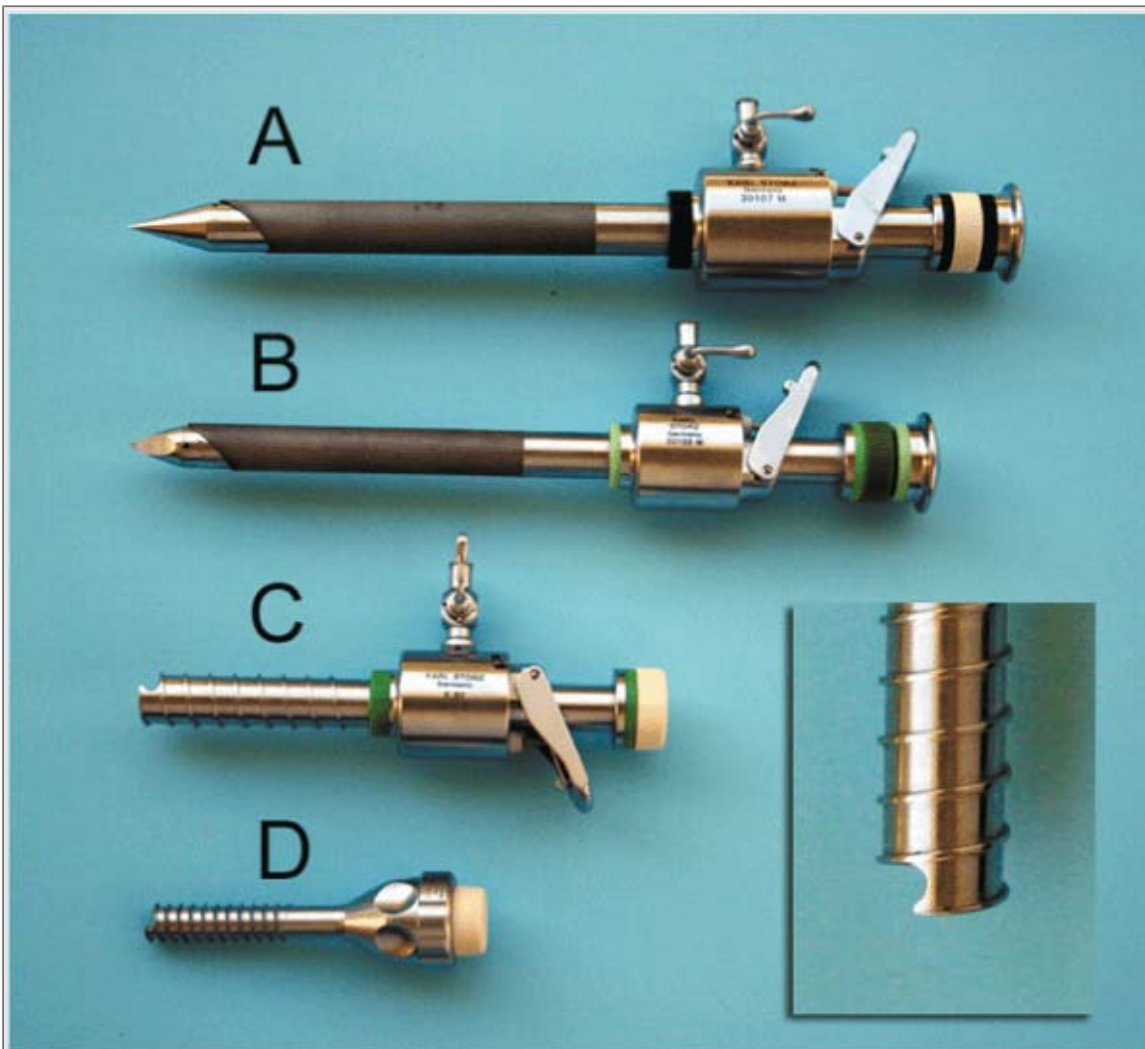


Figure 21.8 Reusable access systems. **A:** is a sharp conical device while **B** represents a pyramidal-tipped design. **C** and **D** (and *inset*) are images of the so-called EndoTip device that can be positioned in the abdominal wall by simply twisting or screwing it in without the requirement of a trocar.

The trocar is a longer instrument of slightly smaller diameter that is passed through the cannula, exposing its tip. Most trocars have sharp tips, allowing penetration of the abdominal wall after a small skin incision. Many disposable trocar-cannula systems are designed with a "safety mechanism"—usually a pressure-sensitive spring that either retracts the trocar or deploys a protective sheath around its tip after passage through the abdominal wall. None of these protective devices has been shown to make insertion safer, however, and they all increase the cost of the equipment.

Following open laparoscopy, cannulas can be inserted either after the successful creation of a pneumoperitoneum (secondary puncture) or without previously instilling intraperitoneal gas (primary puncture). With open laparoscopy, there is less risk of injury to blood vessels. However, open laparoscopy cannot prevent all insertion accidents because intestine can be entered inadvertently no matter how small the incision. There is little evidence that a pneumoperitoneum is necessary, at least in the absence of pre-existing abdominal wall adhesions. Therefore, **in women with no previous surgery, the primary puncture can be performed with a sharp-tipped trocar-cannula system, which reduces operating time. The first, or primary, cannula must be of sufficient caliber to permit passage of the**

laparoscope and usually is inserted in or at the lower border of the umbilicus. The incision should be extended only enough to allow insertion of the cannula; otherwise, leakage of gas may occur around the sheath. The patient should be in an unaltered supine position during placement of the primary cannula. For the primary puncture, either the surgeon or an assistant should elevate the abdominal wall as described previously. Both

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hands can be positioned on the device, using one to provide counterpressure and control to prevent "overshoot" and resultant injury to bowel or vessels. **The angle of insertion is the same as for the insufflation needle; adjustments are made according to the patient's weight and body habitus.** The laparoscope should be inserted to confirm proper intraperitoneal placement before the insufflation gas is allowed to flow. **Previous abdominal surgery increases the incidence of adhesions of the bowel to the anterior abdominal wall, frequently near the umbilicus and in the path of the primary trocar** (8,62). In such patients, another primary insertion site, such as the left upper quadrant, should be selected, even if it is used solely for conveying a narrow "scout" laparoscope, some types of which can be inserted through an insufflation needle (Fig. 21.10). Using such a laparoscope, the presence of adhesions under the incision can be excluded and the umbilical cannula can be inserted under direct vision. If adhesions are noted under the incision, appropriate placement of secondary cannulas may be used to introduce instruments for adhesiolysis. Alternate insertion sites for primary cannulas are shown in Figure 21.6.

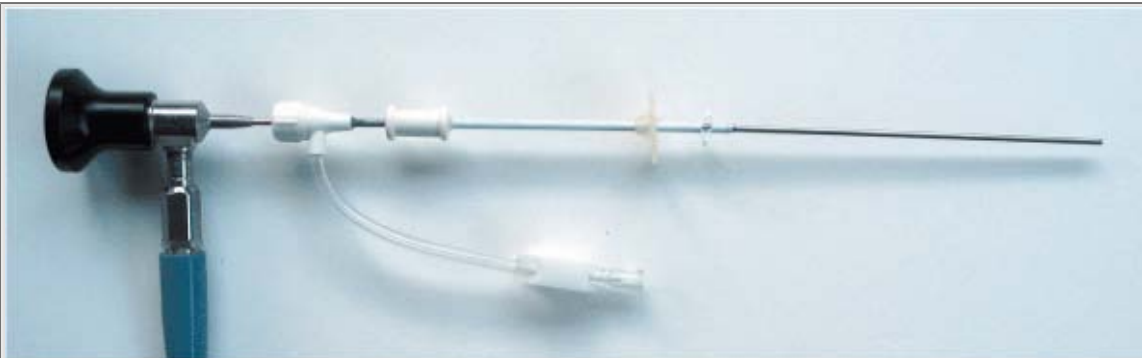


Figure 21.10 "Scout" Laparoscope. The 2-millimeter laparoscope from Figure 21.9 and the 2.7-mm access system from Figure 21.7 are shown here assembled. The tubing is connected to inflow gas, usually carbon dioxide.

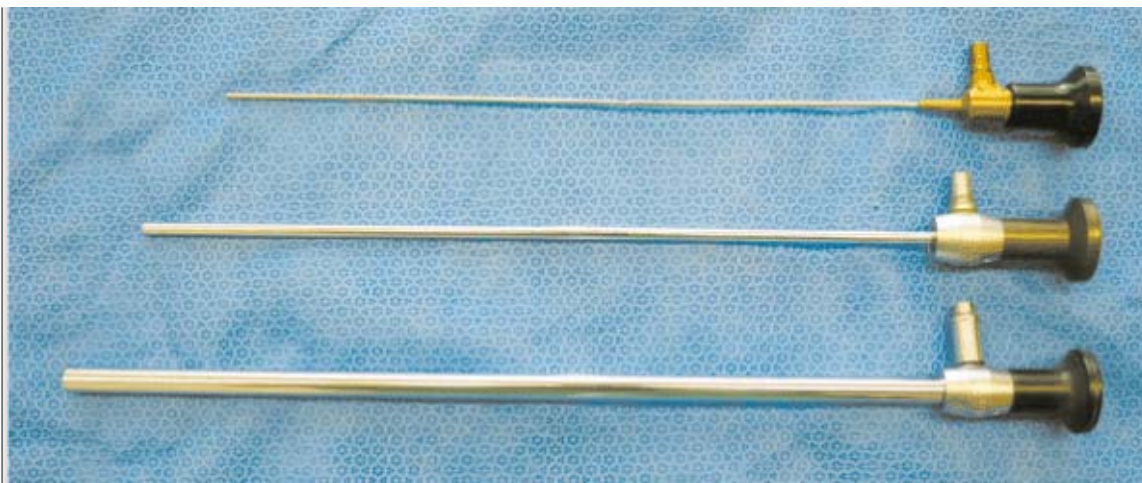


Figure 21.9 Laparoscopes. Three 0-degree laparoscopes are shown. From top to bottom, 2-mm, 5-mm and 10-mm diameter.

Ancillary Cannulas

Ancillary cannulas are necessary to perform most diagnostic and operative laparoscopic procedures. Most currently available disposable ancillary cannulas are identical to those designed for insertion of the primary cannula; however, simple cannulas without safety sheaths and insufflation ports are sufficient (Figs. 21.7D and 21.8D).

Proper positioning of these cannulas depends on a sound knowledge of the abdominal wall vascular anatomy. **For the secondary puncture, the patient should be tipped head**

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down (Trendelenburg), allowing the abdominal contents to move away from the sites for secondary puncture, and thus making it unnecessary to lift the abdominal wall during secondary cannula insertion. Ancillary cannulas should always be inserted under direct vision because injury to bowel or major vessels can occur. Before insertion, the bladder should be drained with a urethral catheter. The insertion sites depend on the procedure, the disease, the patient's body habitus, and the surgeon's preference. For diagnostic laparoscopy, the most useful and cosmetically acceptable site for insertion of an ancillary cannula is in the midline of the lower abdomen, about 2 to 4 cm above the symphysis. The ancillary cannula should not be inserted too close to the symphysis because it limits the mobility of the ancillary instruments and access to the cul-de-sac. Laparoscope cannulas can become dislodged and slip out of the incision during a procedure. There are a variety of cannula attachments, called grippers, designed to prevent slippage.

Lateral placement of lower-quadrant cannulas are useful for operative laparoscopy, but the superficial and inferior epigastric vessels must be located to avoid injury (Fig. 21.3). Transillumination of the abdominal wall from within permits the identification of the superficial inferior epigastric vessels in most thin women. However, the deep inferior epigastric vessels cannot be identified by this mechanism because of their location deep to the rectus sheath. **The most consistent landmarks are the medial umbilical ligaments (obliterated umbilical arteries) and the exit point of the round ligament into the inguinal canal.** At the pubic crest, the deep inferior epigastric vessels can often be visualized between the medially located umbilical ligament and the laterally positioned exit point of the round ligament. The trocar should be inserted medial or lateral to the vessels if they are visualized. **If the vessels cannot be seen and it is necessary to position the cannula laterally, the cannula should be placed 3 to 4 cm lateral to the medial umbilical ligament or lateral to the lateral margin of the rectus abdominis muscle.** If

the insertion is placed too far laterally, it will endanger the deep circumflex epigastric artery. The risk of injury can be minimized by placing a 22-gauge spinal needle through the skin at the desired location, directly observing the entry through the laparoscope. This provides reassurance that a safe location has been identified and allows visualization of the peritoneal needle hole, which provides a precise target for inserting the trocar.

Even after a proper incision, the abdominal wall vessels can be injured if the trocar slides medially during placement. Large-diameter trocars are more likely to cause injury; therefore, the smallest cannulas necessary to perform the procedure should be used. Ancillary cannulas should not be placed too close together because this results in hindrance of the hand instruments, which compromises access and maneuverability.

Visualization

During endoscopy, the image must be transferred through an optical system. Although direct optical viewing is feasible and often used for diagnostic purposes, virtually all operative laparoscopy is performed using video guidance.

Operative versus Diagnostic Equipment

Laparoscopes used for operative purposes have a straight channel, parallel to the optical axis, for the introduction of operating instruments. This provides an additional port for the insertion of instruments and the tangential application of laser energy. However, operative endoscopes are of relatively larger caliber than diagnostic laparoscopes and have smaller fields of view and increased electrosurgical risks. Diagnostic laparoscopes permit better visualization at a given diameter and are associated with fewer electrosurgical risks.

Diameter

Narrow-diameter laparoscopes allow limited transfer of light both into and out of the peritoneal cavity; therefore, they require a more sensitive camera or a more powerful light

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source for adequate illumination. Ideal illumination is provided by 10-mm diagnostic laparoscopes, but improvements in optics are making more procedures feasible with smaller-caliber devices (Fig. 21.9).

Viewing Angle

The viewing angle depicts the relationship of the visual field to the axis of the endoscope and is usually either zero or 30 degrees to the horizontal. The zero-degree scope is the standard for gynecologic surgery. However, the 30-degree angle provides some advantage in difficult situations, such as the performance of retropubic urethropexy or adhesiolysis or for surgery in the presence of large myomas.

Imaging Systems

The video camera captures the image transmitted by the endoscope and the image is transmitted to the body of the camera located outside the operative field, where it is processed and sent to a monitor and, if desired, a recording device (Fig. 21.11). The resolution capability of the monitor should be at least equal to that provided by the camera. Most monitors have the potential to display about 800 horizontal lines of resolution. The more light transmitted through the endoscope, the better the visualization. The best currently available output is achieved from

250 to 300 watts, usually using xenon or metal halide bulbs. Most camera systems are integrated with the light source to vary light output automatically, depending on the amount of exposure required. Light guides or cables transmit light from the source to the endoscope via a bundle densely packed optical fibers (fiberoptic). Fiberoptic cables lose function over time, particularly if they are mishandled, which may break the fibers.





Figure 21.11 Laparoscopic Tower. This tower comprises a monitor (A), a camera body or base unit (B) attached to a camera sensor; a light source (C) attached to a cable, which in turn will be connected with the endoscope; a still-image printer (D) and an insufflation machine (E). A video recorder is shown in (F).

Intraperitoneal Distention

Insufflation Machines

The insufflator delivers CO₂ from a gas cylinder to the patient through tubing connected to one of the ports on the laparoscope. Most insufflators can be set to maintain a predetermined intra-abdominal pressure. High flow rates (9–20 L/min) are especially useful for maintaining exposure when suction of smoke or fluid depletes the volume of intraperitoneal gas.

Laparoscopic Lifting Systems

Intraperitoneal retractors attached to a pneumatic or mechanical lifting system can be used to create an intraperitoneal space much like a tent. This “gasless” or “apneumatic” technique may have some advantages over pneumoperitoneum, particularly in patients with cardiopulmonary disease. Airtight cannulas are not necessary, and instruments do not need to have a uniform, narrow, cylindrical shape. Consequently, some conventional instruments may be used directly through the incisions.

Fluid Management

Fluid may be instilled into the peritoneal cavity through wide-caliber arthroscopy or cystoscopy tubing using pressure provided by gravity, an infusion cuff, or a high-pressure mechanical pump. The pumps deliver fluid faster than the other techniques, and the highly pressurized stream of fluid may facilitate blunt dissection (hydro- or aquadissection). Small volumes of fluid can be removed with a syringe attached to a cannula; for large volumes, it is necessary to use suction generated by a machine or a wall source.

The cannulas used for suction and irrigation depend on the irrigation fluid used and the fluid being removed. For ruptured ectopic gestations or other procedures in which there is a large amount of blood and clots, large-diameter cannulas (7–10 mm) are preferred. Cannulas with narrow tips are more effective in generating the high pressure needed for hydrodissection.

If large volumes of fluid are required, isotonic fluids should be used to avoid fluid overload and electrolyte imbalance. If electrosurgery is to be performed, however, small volumes of a nonelectrolyte-containing solution such as glycine or sorbitol can be used for hemostasis and irrigation. *Heparin* (1,000–5,000 U/L) can be added to irrigating solution to prevent blood from clotting, thus allowing it to be removed more easily.

Tissue Manipulation

Uterine Manipulators

A properly designed uterine manipulator should have an intrauterine component, or obturator, and a method for fixation of the device to the uterus. Articulation of the instrument permits acute anteversion or retroversion, both of which are extremely useful maneuvers. If the uterus is large, longer and wider obturators are used so that the manipulations can be performed more effectively. Two types of uterine manipulators are shown in Figure 21.12. A hollow obturator attached to a port allows intraoperative instillation of liquid dye to demonstrate tubal patency.



Figure 21.12 Uterine Manipulators. (Top) is the disposable "V-Care" device. At the tip is a balloon inflated to maintain the device in the endometrial cavity. Next to the tip is a cervical collar that serves to facilitate identification of the vaginal fornices and cutting of the vagina in laparoscopic total hysterectomy. The blue truncated cone maintains a seal so that gas won't leak out when culdotomy is performed. (Bottom) is the reusable Pelosi manipulator. The ring handle allows the surgeon to antevert the uterus.

Grasping Forceps

The forceps used during laparoscopy should replicate those used in open surgery. Disposable instruments generally do not have the quality, strength, and precision of nondisposable forceps (Fig. 21.13). Instruments with teeth (toothed forceps) are necessary to grasp the peritoneum or the edge of ovary securely to remove an ovarian cyst. Minimally traumatic instruments designed like Babcock clamps are needed to retract the fallopian

tube safely. Tenaculum-like instruments are desirable to retract leiomyomas or the uterus. A ratchet is useful to hold tissue without arduous hand pressure. Graspers should be insulated if unipolar electrical energy is being used for hemostasis.

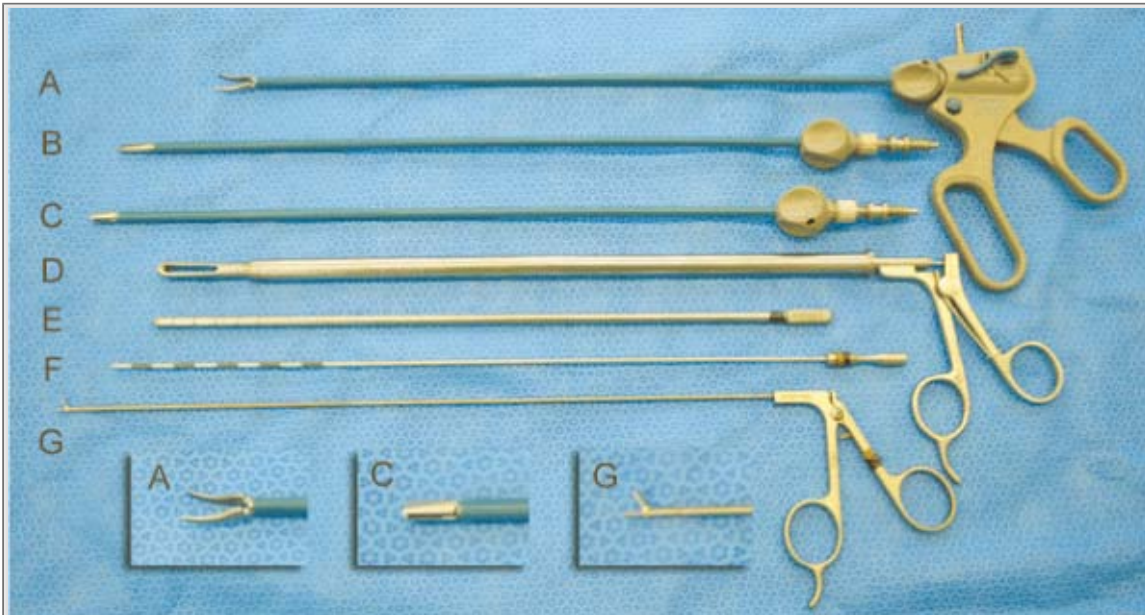


Figure 21.13 Laparoscopic Instruments for Grasping and Manipulating Tissue. **A:** (*top and inset*) are 5-mm diameter graspers with a curved tip, often called “Maryland” graspers. Other reusable tips (**B**) and (**C**) may be positioned in the same handle as is shown for **A**. **D:** is a 10-mm claw grasper while (**E**) and (**F**) are 5- and 2-mm manipulating probes respectively. **G:** is a 2-mm grasping forceps.

Cutting, Hemostasis, and Tissue Fixation

Cutting can be achieved by mechanical means or by using radiofrequency electrical current, laser energy, or ultrasonic energy. The methods for maintaining or securing hemostasis include sutures, clips, linear staplers, energy sources, and topical or injectable substances. Secure apposition or tissue fixation may be accomplished with sutures, clips, or staples. With appropriate training, a skilled surgeon can obtain good results with any combination of these techniques for cutting, hemostasis, and tissue fixation. Studies in animals have not demonstrated any difference in injury characteristics when cutting is performed with either laser or radiofrequency energy (44,45,63), and randomized controlled studies have shown no differences in fertility outcomes (64). Therefore, differences in results are more likely to be caused by other factors, such as patient selection, extent of disease, and degree of surgical expertise.

Cutting

The most useful cutting instruments are scissors (21.14 Bottom). Because it is difficult to sharpen laparoscopic scissors, most surgeons prefer disposable instruments that can be used until dull and then discarded. Another mechanical cutting tool is the linear stapler–cutter that can simultaneously cut and hemostatically staple the edges of the incision. The cost and large dimensions of the instruments limit their practical use to only a few highly selected situations, such as separation of the uterus from the ovary and fallopian tube during laparoscopic hysterectomy.

Laser and electrical sources of energy manifest their effect by conversion

of electromagnetic energy generated by a special electro-surgical unit (ESU) (Fig. 21.15) to mechanical energy which is then transformed to thermal energy. Highly focused radiofrequency energy produces vaporization or cutting, whereas less focused energy (high-current density) raises the intracellular temperature above 100° C and results in tissue vaporization or, if the instrument is moved in a linear fashion, tissue cutting. Less focused radiofrequency energy (moderate current density) elevates intracellular temperature, causing desiccation and tissue coagulation, but vaporization and cutting does not occur. Electro-surgical instruments that are narrow or pointed are capable of generating the high-power densities necessary to vaporize or cut tissue. Continuous or modulated, usually unipolar, outputs are used. For optimal results, they should be used in a noncontact fashion, following (not leading) the energy. Specially designed bipolar cutting probes are available that have one integrated electrode shaped as a needle and the other band-shaped electrode designed to be dispersive (Fig. 21.14 Top). Laparoscopic scissors with unipolar or bipolar electro-surgical attachments are designed to cut mechanically, and energy may be applied simultaneously for desiccation and hemostasis when cutting tissue that contains small blood vessels (Fig. 21.14 Bottom).



Figure 21.14 Laparoscopic Cutting Devices. *Top and inset left* is a bipolar electro-surgical spatula. *Middle and center inset* is a harmonic scalpel. This device oscillates at 55,000 Hz to cut tissue. *Bottom and inset right* are laparoscopic scissors. They may be connected if desired to an electro-surgical generator to act as a unipolar electrode.

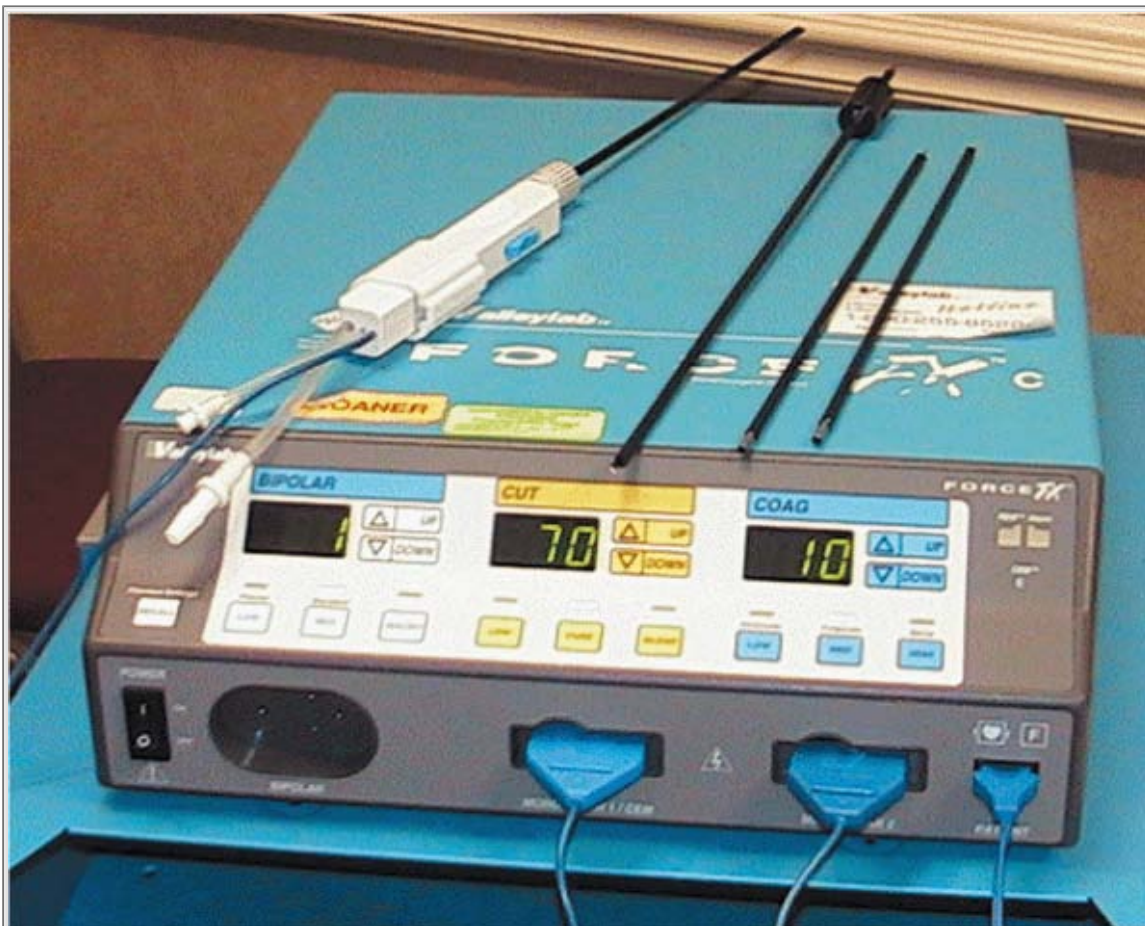


Figure 21.15 Radiofrequency Electrosurgical Generator. Displayed is the Force FX generator with unipolar laparoscopic electrodes. The device is capable of outputting high-voltage ("coagulation") and low-voltage ("cut") waveforms for unipolar instruments as well as a low-voltage bipolar circuit for bipolar instruments.

Laser energy can be focused to vaporize and cut tissue. The most efficient laser-based cutting instrument is the CO₂ laser, which has the drawback of requiring linear transmission because light cannot be conducted effectively along bendable fibers. The potassium-titanyl-phosphate (KTP) and neodymium:yttrium, aluminum, garnet (Nd:YAG) lasers are also effective cutting tools. They are capable of propagating energy along bendable quartz fibers but have a slightly greater thermal injury risk than electrical or CO₂ laser energy. Because of such limitations and their additional expense, these lasers are of limited value.

Ultrasonic cutting is largely accomplished mechanically using a blade that oscillates back and forth in a linear fashion (Fig. 21.14 Center). The oscillation is achieved using a vibrating element located in a handle that vibrates the blade, hook, or clamp 55,000 times per second (55 kHz). The distance of the oscillation can be varied and determines the rapidity

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of the cutting process. The tip of the device cuts mechanically, but there is a degree of collateral thermal tissue coagulation injury that can be used for hemostasis. In low-density tissue, the process of mechanical cutting is augmented by the process of cavitation, in which reduction of local atmospheric pressure allows vaporization of intracellular water at body temperature.

Hemostasis

Because of the visual, tactile, and mechanical limitations of laparoscopy, prevention of bleeding is important for efficient, effective, and safe procedures.

Radiofrequency electricity is the least expensive and most versatile method for achieving hemostasis during laparoscopy and can be applied with either monopolar or bipolar instruments. Regardless of the type of system, the process of electrical desiccation and coagulation is best achieved by contacting the tissue and activating the electrode using continuous low-voltage or "cutting" current. With adequate power, typically 25 watts, tissue will be heated and coagulated. Blood vessels should be compressed with the blades of the forceps before the electrode is activated so that the "heat sink" effect of flowing blood is eliminated. This also allows the opposing walls of the vessel to bond together, forming a strong tissue seal in a process called *coaptive coagulation*. Bipolar devices can be fitted with a serial ammeter that measures the current flowing through the system. When the tissue between the blades of the forceps is completely desiccated, the device is no longer able to conduct electricity, which can trigger a visual or auditory cue for the surgeon. Alternatively, the generator can be designed to stop automatically when current is no longer being conducted by the tissue between the blades of the forceps. The surgeon can reduce lateral thermal spread of radiofrequency energy by manually pulsing delivery or by simultaneously running irrigation fluid over the pedicle. Automated generators that pulse energy automatically are available and such bipolar systems can include mechanical blades to cut tissues following coagulation of the tissue (Fig. 21.16).

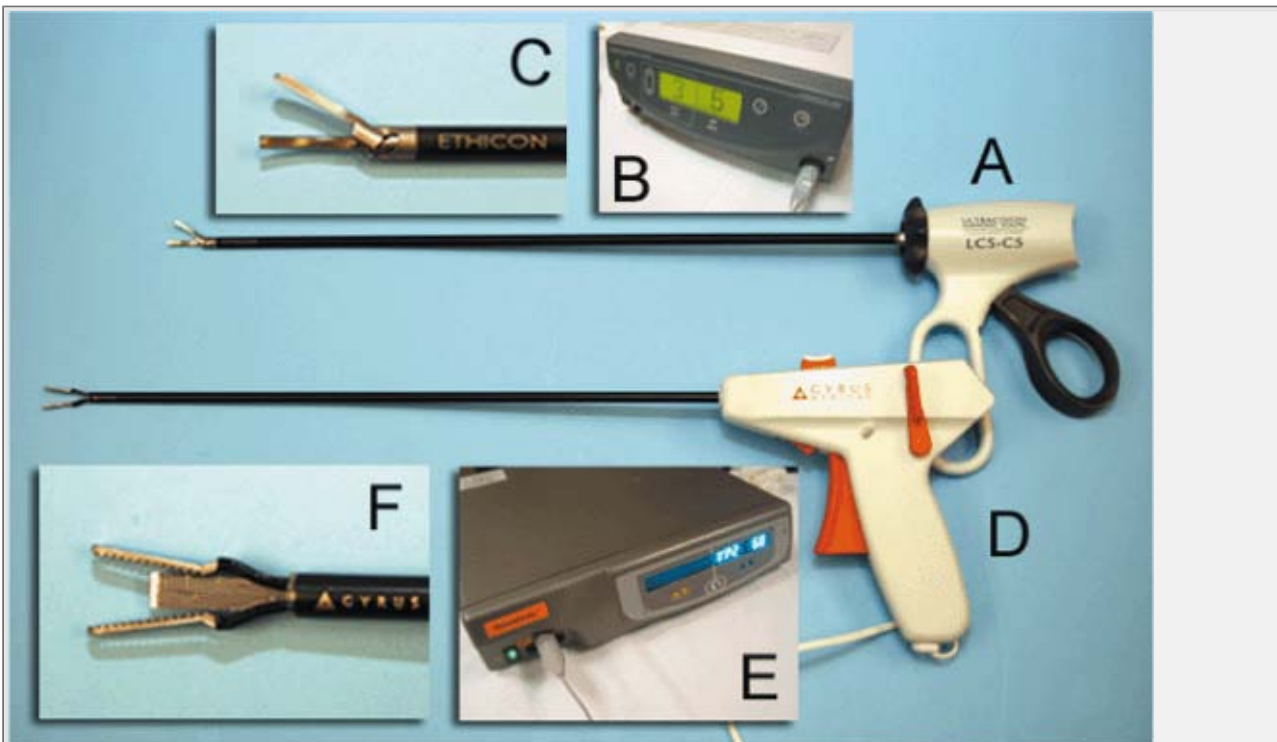


Figure 21.16 Displayed are two devices that both cut and coagulate or seal tissue. Top (A–C) are the ligating cutting shears (LCS) that are based on the same technology as the harmonic scalpel displayed in Figure 21.13. The bottom blade oscillates (C) while the top blade is opened to grasp the tissue and then used by the surgeon to slowly transect and seal the blood vessels in the tissue being transected. The PlasmaKinetic (D–F) is a bipolar radiofrequency device that, using electrical impedance, tells the surgeon when the tissue is coagulated. Then the orange trigger (*top*) is pushed deploying the blade (F), thereby cutting the coagulated tissue.

Control of superficial bleeding can be achieved with fulguration, the near-contact spraying of tissue with unipolar, high-voltage radiofrequency energy from the "coagulation" side of the electrosurgical generator. Care must be taken to perform laparoscopic fulguration carefully, ensuring that the entire shaft of the laparoscopic instrument is well away from bowel.

Ultrasonic instruments can be used for hemostasis as well. Those with a forcepslike end disperse the mechanical energy in a way that allows the tissue to be heated and coagulated. These so called "ligating-cutting" shears also cut when high pressure is exerted in the handle by the surgeon (Fig. 21.16 A-C).

Clips may be used with specially designed laparoscopic instruments. Nonabsorbable clips made of titanium are useful for relatively narrow vessels, and longer, self-retaining clips are generally preferred for larger vessels. Clips may be of particular value when securing relatively large vessels near an important structure such as the ureter.

Laparoscopic suturing is a method of maintaining hemostasis (65). Compared with clips or linear staplers, suturing has a relatively low cost of materials, although operating time may be longer. **The two basic methods for securing a ligature around a blood vessel are intracorporeal and extracorporeal knots, depending on where the suture is tied. Intracorporeal knots replicate the standard instrument-tied knot and are formed within the peritoneal cavity. Extracorporeal knots are created outside the abdomen under direct vision and then transferred into the peritoneal cavity by knot manipulators** (see Fig. 21.17) (66). Pretied knotted suture loops attached to long introducers, called endoloops, may also be used to secure vascular pedicles. However, care should be taken to make sure that they are tightly secured and that no other tissue is incorporated in the loop.

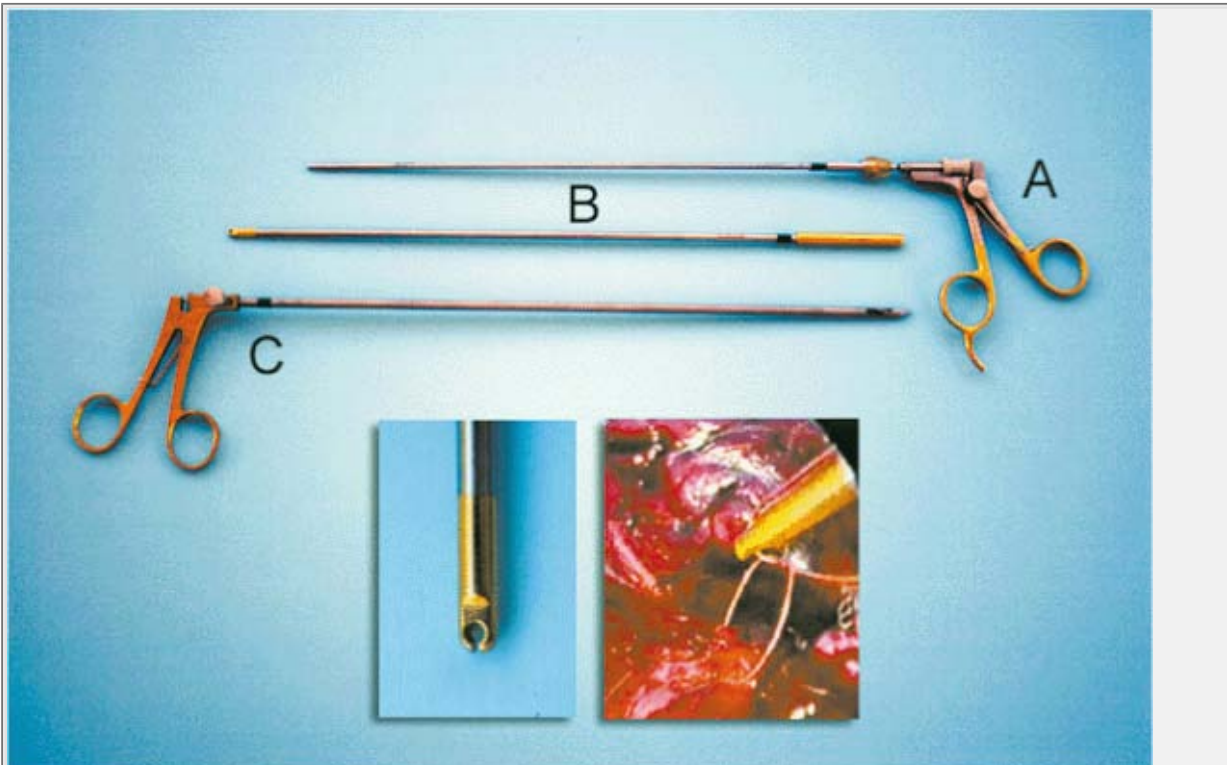


Figure 21.17 Laparoscopic Suturing Instruments. 3-mm and 5-mm diameter laparoscopic needle drivers are displayed in **A** and **C** while a knot manipulator is shown in **B** and inset left. The device is shown transferring a knot into the peritoneal cavity (*inset right*).

Topical agents such as microfibrillar collagen are available in 5-mm and 10-mm diameter laparoscopic applicators (see Fig. 21.13). Local injection of diluted vasopressin may be used to maintain hemostasis for myomectomy or removal of ectopic pregnancy.

Removal of Tissue

After excising tissue, it is usually necessary to remove it from the peritoneal cavity. Small samples can be pulled through an appropriate-sized cannula with grasping forceps; however, larger specimens may not fit. If the specimen is cystic, it may be drained by a needle or incised, shrinking it to a size suitable for removal through the cannula or one of the small laparoscopic incisions. **If there is any concern for malignancy, an alternative is to place the specimen in an endoscopic retrieval bag before drainage to prevent spillage** (Fig. 21.18). More solid tissue may be morcellated with scissors, ultrasonic equipment, or electrosurgery. If monopolar radiofrequency instruments are used for electrosurgical morcellation, the specimen must remain attached to the patient to preserve the integrity of the electrical circuit. Alternatively, special bipolar needles are available that do not require a dispersive electrode.





Figure 21.18 Specimen Removal Bag. This 10-mm diameter bag is positioned in the peritoneal cavity. Then, the bag is deployed (*insets*), allowing the surgeon to place specimens for removal.

Larger specimens may be removed by inserting a larger cannula through an incision in the cul-de-sac (posterior culdotomy) or by extending one of the laparoscopy incisions. With the exception of colpotomy, extension of the umbilical incision may be the most cosmetic approach because removal of the tissue can be directed from an endoscope positioned in

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one of the ancillary ports. Electronic morcellators are available to remove large tissue specimens by reducing them to smaller sections (Fig. 21.19). These are especially useful for laparoscopic myomectomy and laparoscopic supracervical hysterectomy.



Figure 21.19 Electromechanical Morcellator. This device is positioned in the peritoneal cavity and attached to the power generator (*inset*). The blunt obturator is removed; a grasping instrument inserted through the lumen is used to withdraw the tissue, which is cut by a cylindrical blade. The motor is activated by a foot pedal.

Incision Management

Dehiscence and hernia risk appear to significantly increase when the fascial incision is larger than 10 mm in diameter (67). Closure of the fascia should take place under direct laparoscopic vision to prevent the accidental incorporation of bowel into the incisions, and the peritoneum should be included to reduce the risk of Richter's hernia. A small-caliber laparoscope passed through one of the narrow cannulas can be used to direct the fascial closure using curved needles or a ligature carrier especially designed for this purpose.

Complications

Patients recovering from laparoscopic surgery usually feel better every day. Pain diminishes, gastrointestinal function improves rapidly, and fever is extremely unusual. Therefore, if a patient's condition is not improving, possible complications of anesthesia or surgery should be considered. Laparoscopic procedures can be complicated by infections, trauma, or hemorrhage, as well as by problems associated with anesthetic use. The incidence of infection is lower than with procedures performed by laparotomy. Conversely, problems associated with visualization in conjunction with the change in anatomic perspective may increase the risk of damage to blood vessels or vital structures such as the bowel, ureter, or bladder.

Anesthetic and Cardiopulmonary Complications

A recent review of laparoscopic tubal sterilization in 9,475 women found no deaths from complications of anesthesia (68). However, the potential risks of general anesthesia include hypoventilation, esophageal intubation, gastroesophageal reflux, bronchospasm, hypotension, narcotic overdose, cardiac arrhythmias, and cardiac arrest. These risks can

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be enhanced by some of the inherent features of gynecologic laparoscopy. For example, the Trendelenburg position, in combination with the increased intraperitoneal pressure provided by pneumoperitoneum, places greater pressure on the diaphragm, increasing the risk of hypoventilation, hypercarbia, and metabolic acidosis. This position, combined with anesthetic agents that relax the esophageal sphincter, promotes regurgitation of gastric content, which in turn can lead to aspiration, bronchospasm, pneumonitis, and pneumonia. Parameters of cardiopulmonary function associated with both CO₂ and N₂O insufflation include reduced PO₂, O₂ saturation, tidal volume, and minute ventilation and increased respiratory rate. The use of intraperitoneal CO₂ as a distention medium is associated with an increase in PCO₂ and a decrease in pH. Elevation of the diaphragm may be associated with basilar atelectasis, resulting in right-to-left shunt and a ventilation—perfusion mismatch (69).

Carbon Dioxide Embolus

Carbon dioxide is the most widely used peritoneal distention medium, largely because the rapid absorption of CO₂ in blood reduces the significance of gas emboli. However, if large amounts of CO₂ gain access to the central venous circulation, if peripheral vasoconstriction occurs, or if the splanchnic blood flow is decreased by excessively high intraperitoneal pressure, severe cardiorespiratory compromise may result.

The signs of CO₂ embolus include sudden and otherwise unexplained hypotension, cardiac arrhythmia, cyanosis, and heart murmurs. The end-tidal CO₂ level may increase, and findings consistent with pulmonary edema may manifest. Accelerating pulmonary hypertension may occur, resulting in right-sided heart failure.

Because gas embolism may result from direct intravascular injection through an insufflation needle, the proper placement of the insufflation needle, if used, must be ensured. Although the initial intraperitoneal pressure may be set at 20 to 30 mm Hg for port placement, it should be maintained at 8 to 12 mm for the rest of the case. The risk of CO₂ embolus also is reduced by careful hemostasis because open venous channels are the portal of entry for gas into the systemic circulation. The anesthesiologist should continuously monitor

the patient's color, blood pressure, heart sounds, heartbeat, and end-tidal CO₂ to allow early recognition of the signs of CO₂ embolus.

If CO₂ embolus is suspected or diagnosed, the surgeon must evacuate the CO₂ from the peritoneal cavity and place the patient in the left lateral decubitus position, with the head below the level of the right atrium. A large-bore central venous line should be inserted immediately to allow aspiration of gas from the heart. Because the findings are nonspecific, the patient should be evaluated for other causes of cardiovascular collapse.

Cardiovascular Complications

Cardiac arrhythmias occur relatively frequently during laparoscopic surgery and are related to a number of factors, the most significant of which are hypercarbia and acidemia. Early reports of laparoscopy-associated arrhythmia were associated with spontaneous respiration; therefore, most anesthesiologists have adopted the practice of mechanical ventilation during laparoscopic surgery. The incidence of hypercarbia is reduced by operating with intraperitoneal pressures at levels less than 12 mm Hg (70).

The risk of cardiac arrhythmia also may be reduced by using NO₂ as a distending medium (see the preceding discussion on Access). Although NO₂ is associated with a decreased incidence of arrhythmia, it also is insoluble in blood and, therefore, its use may increase the risk of gas embolus. External lifting systems avoid the complication of hypercarbia and can also provide protection against cardiac arrhythmia.

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Hypotension can occur because of decreased venous return secondary to very high intraperitoneal pressure, and this condition may be potentiated by volume depletion. Vagal discharge may occur in response to increased intraperitoneal pressure, which can cause hypotension secondary to cardiac arrhythmias (71). All of these side effects should be considered when performing surgery on patients with pre-existing cardiovascular disease.

Gastric Reflux

Gastric regurgitation and aspiration can occur during laparoscopic surgery, especially in patients with obesity, gastroparesis, hiatal hernia, or gastric outlet obstruction. In these patients, the airway must be maintained with a cuffed endotracheal tube, and the stomach must be decompressed (e.g., with a nasogastric tube). The lowest necessary intraperitoneal pressure should be used to minimize the risk of aspiration. Patients should be moved out of the Trendelenburg position before being extubated. Routine preoperative administration of *metoclopramide*, H₂-blocking agents, and nonparticulate antacids also reduces the risk of aspiration.

Extraperitoneal Insufflation

The most common causes of extraperitoneal insufflation are preperitoneal placement of the insufflating needle and leakage of CO₂ around the cannula sites. Although this condition is usually mild and limited to the abdominal wall, subcutaneous emphysema can become extensive, involving the extremities, the neck, and the mediastinum. Another relatively common site for emphysema is the omentum or mesentery, a circumstance that may be mistaken for preperitoneal insufflation.

Subcutaneous emphysema may be identified by the palpation of crepitus, usually in the

abdominal wall. Emphysema can extend along contiguous fascial plains to the neck, where it can be visualized directly. Such a finding may reflect mediastinal emphysema, which may indicate impending cardiovascular collapse (72,73,74).

The risk of subcutaneous emphysema is reduced by the proper positioning of the insufflation needle and by maintaining a low intraperitoneal pressure after placement of the desired cannulas. Other approaches that reduce the chance of subcutaneous emphysema include open laparoscopy and the use of abdominal wall lifting systems that make gas unnecessary.

If the insufflation has occurred extraperitoneally, the laparoscope can be removed and the procedure can be repeated. However, difficulty may ensue because of the altered anterior peritoneum. Open laparoscopy or the use of an alternate site, such as the left upper quadrant, should be considered. One approach is to leave the laparoscope in the expanded preperitoneal space while the insufflation needle is reinserted under direct vision through the peritoneal membrane caudad to the tip of the laparoscope (75).

In mild cases of subcutaneous emphysema, the findings quickly resolve after evacuation of the pneumoperitoneum, and no specific intraoperative or postoperative therapy is required. When the extravasation extends to the neck, it is usually preferable to terminate the procedure because pneumomediastinum, pneumothorax, hypercarbia, and cardiovascular collapse may result. Following termination of the procedure, it is prudent to obtain a chest x-ray. The patient's condition should be managed expectantly unless a tension pneumothorax results, in which case immediate evacuation must be performed using a chest tube or a wide-bore needle (14-16 gauge) inserted in the second intercostal space in the midclavicular line.

Electrosurgical Complications

Complications of electrosurgery occur secondary to thermal injury from unintended or inappropriate use of the active electrode, current diversion to an undesirable path,

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and injury at the site of the dispersive electrode. Such complications may occur with the use of these instruments during laparoscopic, abdominal, or vaginal surgery. Active electrode injury can occur with either unipolar or bipolar instruments, whereas trauma secondary to current diversion and dispersive electrode accidents occur only with unipolar devices. Complications of electrosurgery are reduced by adherence to safety protocols coupled with a sound understanding of the principles of electrosurgery and the circumstances that can lead to injury (17).

Active Electrode Trauma

If the foot pedal is accidentally depressed, tissue adjacent to the electrode will be traumatized. Potential sites of injury include the bowel, ureter, or, if the electrode lies on the abdomen, the skin. Injury from direct extension of thermal effect can occur when the zone of vaporization or coagulation extends to large blood vessels or vital structures such as the bladder, ureter, or bowel. Bipolar instruments may reduce but do not eliminate the risk of thermal injury to adjacent tissue (76). Therefore, blood vessels should be isolated before desiccation, especially when they are near vital structures, and appropriate amounts of energy must be applied to allow an adequate margin of noncoagulated tissue.

The diagnosis of direct thermal visceral injury may be difficult. If unintended activation of the electrode occurs, nearby intraperitoneal structures should be evaluated carefully. The appearance can be affected by several factors, including the output of the generator, the type of electrode, its proximity to tissue, and the duration of its activation. The diagnosis of

visceral thermal injury is often delayed until signs and symptoms of fistula or peritonitis appear. Because these complications may not manifest until 2 to 10 days after surgery, patients should be advised to report any postoperative fever or increasing abdominal pain.

Thermal injury to the bowel, bladder, or ureter that is recognized at the time of laparoscopy should be managed immediately, taking into consideration the potential extent of the zone of coagulative necrosis (77). Incisions made with the focused energy from a pointed electrode are associated with a minimal amount of surrounding thermal injury. Prolonged or even transient contact with a relatively large-caliber electrode may produce thermal necrosis that extends several centimeters. In such cases, wide excision or resection will be necessary. The choice of route of access for any required surgical repairs depends in part on the nature of the injury and on the skills and training of the surgeon.

The incidence of unintended activation injuries can be reduced if the surgeon is always in direct control of electrode activation and if all electrosurgical hand instruments are removed from the peritoneal cavity when not in use. When removed from the peritoneal cavity, the instruments should be detached from the electrosurgical generator, or they should be stored in an insulated pouch near the operative field. These measures prevent damage to the patient's skin if the electrode is accidentally activated.

Current Diversion

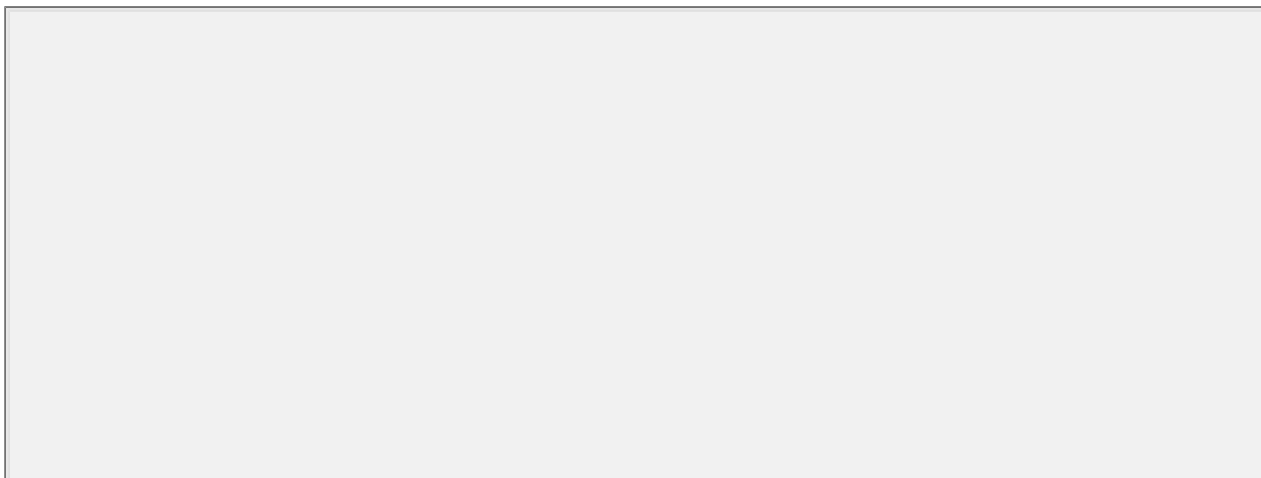
Current diversion occurs when the radiofrequency circuit follows an unintended path between the active electrode and the electrosurgical generator. This may occur with insulation defects, direct coupling, or capacitive coupling. In older, grounded systems, current can be diverted if any part of the patient's body touches a conductive and grounded object. In any of these situations, if the power density becomes high enough, unintended and severe thermal injury can result.

Insulation Defects

If the insulation coating the shaft of an electrosurgical electrode becomes defective, it can allow current diversion to adjacent tissue, often bowel, potentially resulting in significant

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injury (Fig 21.20A). Therefore, the instruments should be examined before each procedure to detect worn or obviously defective insulation. **When using monopolar laparoscopic instruments, the shaft of the device should be kept away from vital structures and, if possible, totally visible in the operative field.**



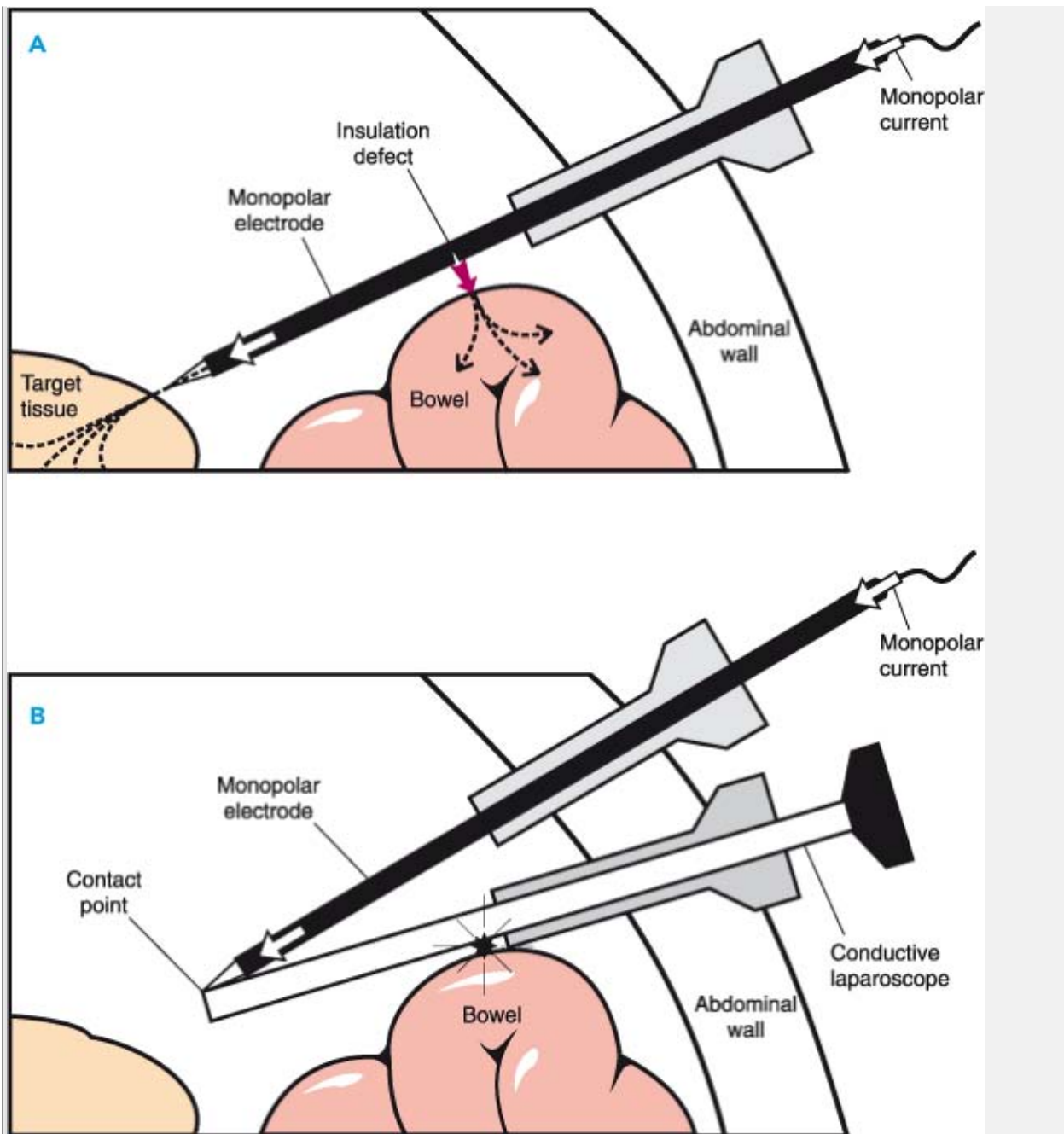


Figure 21.20 Current Diversion Secondary to Insulation Defects and Direct Coupling.

These events may occur with the use of monopolar instrumentation when there is a defect in the insulation (**A**) or, classically, to contact a conductive instrument that, in turn, touches other intraperitoneal structures. In the example depicted (**B**), the active electrode is touching the laparoscope, and current is transferred to bowel through a small enough contact point that thermal injury results. Another common target of such coupling is to noninsulated hand instruments.

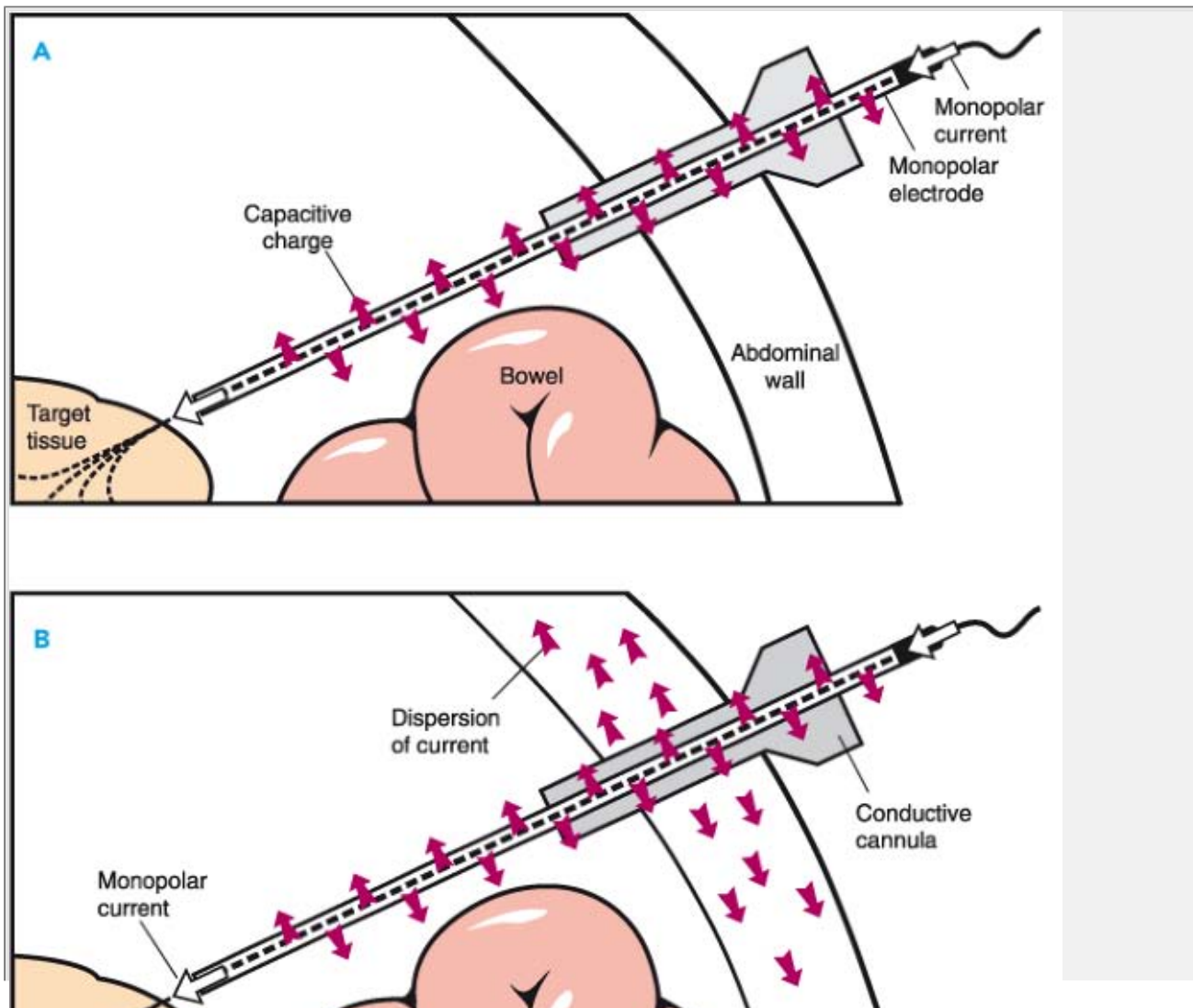
Direct Coupling

Direct coupling occurs when an activated electrode touches and energizes another uninsulated metal conductor such as a laparoscope, cannula, or other instrument. Direct coupling is often used for hemostasis when a grasping instrument is used to occlude a blood vessel while a separate activated electrode is used to provide the energy for desiccation and coagulation. If this occurs while the noninsulated device rests against structures such as bowel or the urinary tract, however, unintended injury may occur (Fig 21.20B). The risk of direct coupling can be

reduced by eliminating the simultaneous use of noninsulated instruments and monopolar electrodes. Furthermore, the surgeon should visually confirm that there is no contact with other conductive instruments before activating a monopolar electrode.

Capacitive Coupling

Capacitance is the ability of a conductor to establish an electrical current in an unconnected but nearby circuit. An electrical field is established around the shaft of any activated unipolar electrode (including the cord), a circumstance that makes the electrode a potential capacitor. This field is harmless if the circuit is completed through a dispersive, low-power density pathway (Fig. 21.21). For example, if capacitive coupling occurs between a laparoscopic electrode and a metal cannula positioned in the abdominal wall, the current is harmlessly dispersed in the abdominal wall at the point where it connects with the dispersive electrode (Fig. 21.21A). However, if the metal cannula is anchored to the skin by a nonconductive plastic retaining sleeve or "gripper" (a hybrid system), the current cannot return to the abdominal wall because the sleeve acts as an insulator (Fig. 21.21B). Instead, the capacitor will have to "look" elsewhere to complete the circuit. Therefore, bowel or any other nearby conductor can become the target of a relatively high-power density discharge (Fig. 21.21C). This mechanism can also occur when a unipolar electrode is inserted through an operating laparoscope that, in turn, is passed through a nonconductive plastic laparoscopic cannula. In this configuration, the plastic port acts as the insulator. If the electrode capacitively couples with the metal laparoscope, nearby bowel will be at risk for significant thermal injury (78).



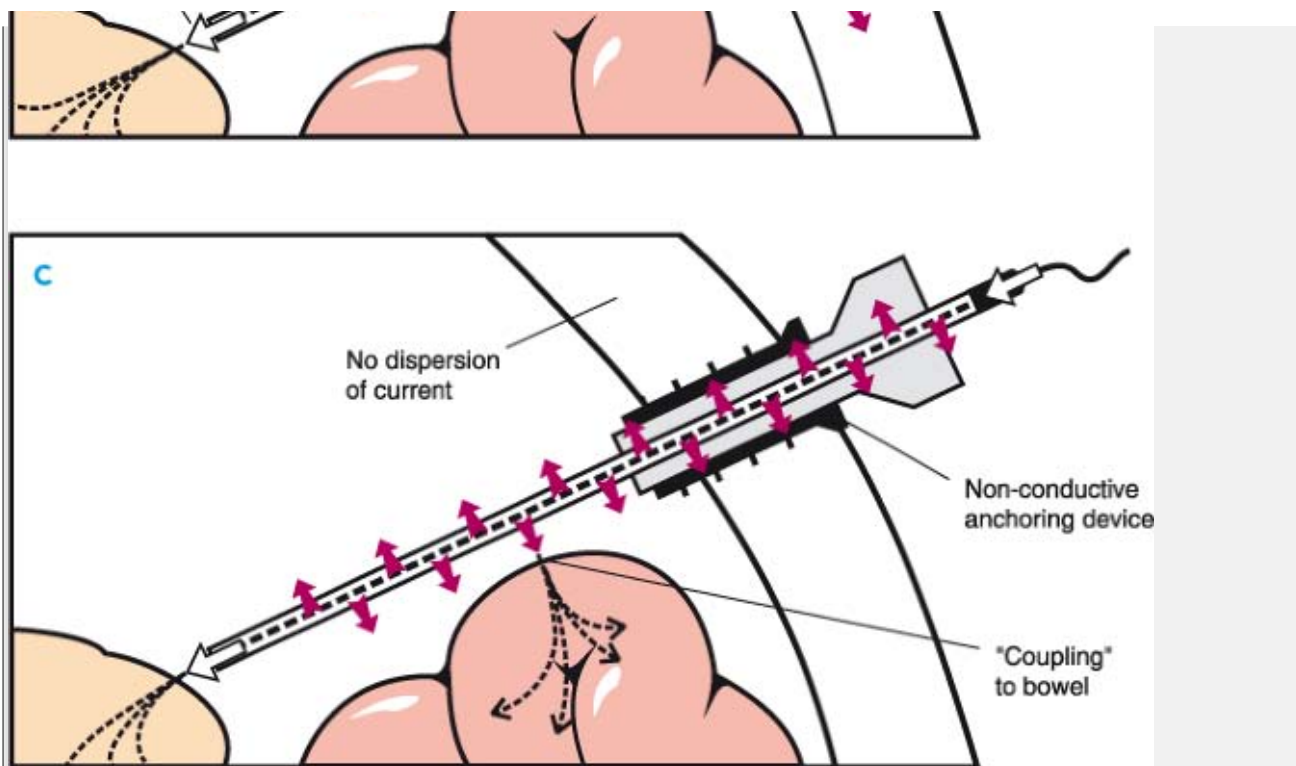


Figure 21.21 Capacitive coupling. **A:** All activated monopolar electrodes emit a surrounding charge, proportional to the voltage of the current. This makes the electrode a potential capacitor. **B:** Generally, as long as the charge is allowed to disperse through the abdominal wall, no sequelae result. However, if the “return” to the dispersive electrode is blocked by insulation, such as a plastic anchor (**C**), the current can couple to a conductive cannula or directly to bowel.

Capacitive coupling can be prevented by avoiding the use of hybrid laparoscope-cannula systems that contain a mixture of conductive and nonconductive elements. Instead, the use of all-plastic or all-metal cannula systems is preferred. When operating laparoscopes are used, all-metal cannula systems should be the rule unless there is no intent to perform unipolar electro-surgical procedures through the operating channel.

Dispersive Electrode Burns

Modern electro-surgical units are designed with isolated circuits and impedance monitoring systems that shut down the machine if dispersive electrode detachment (“patient pad”) occurs. The use of isolated-circuit electro-surgical generators with dispersive electrode monitors has virtually eliminated dispersive electrode-related thermal injury. Dispersive electrode monitoring is actually accomplished by measuring the impedance in the dispersive electrode, which should always be low because of the large surface area. Without such devices, partial detachment of the dispersive electrode could result in a thermal injury because reducing the surface area of the electrode raises the current density (Fig. 21.22).

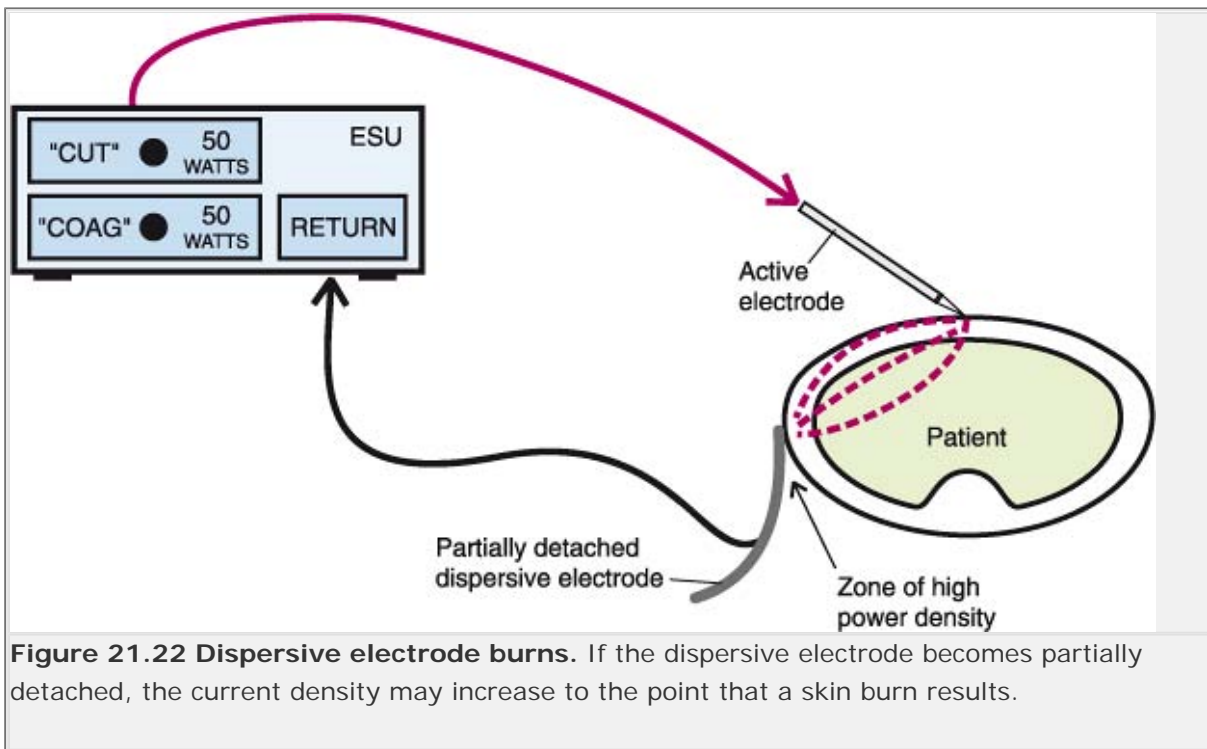


Figure 21.22 Dispersive electrode burns. If the dispersive electrode becomes partially detached, the current density may increase to the point that a skin burn results.

Because ground-referenced machines without such safeguards are still in use, it is important to know the type of electrosurgical unit used in the operating room. If the electrosurgical generator is ground referenced and if the dispersive electrode becomes detached,

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unplugged, or otherwise ineffective, the current seeks any grounded conductor, such as electrocardiograph patch electrodes or the conductive metal components of the operating table (Fig. 21.23). If the conductor has a small surface area, the current or power density may become high enough to cause thermal injury (Fig. 21.24).

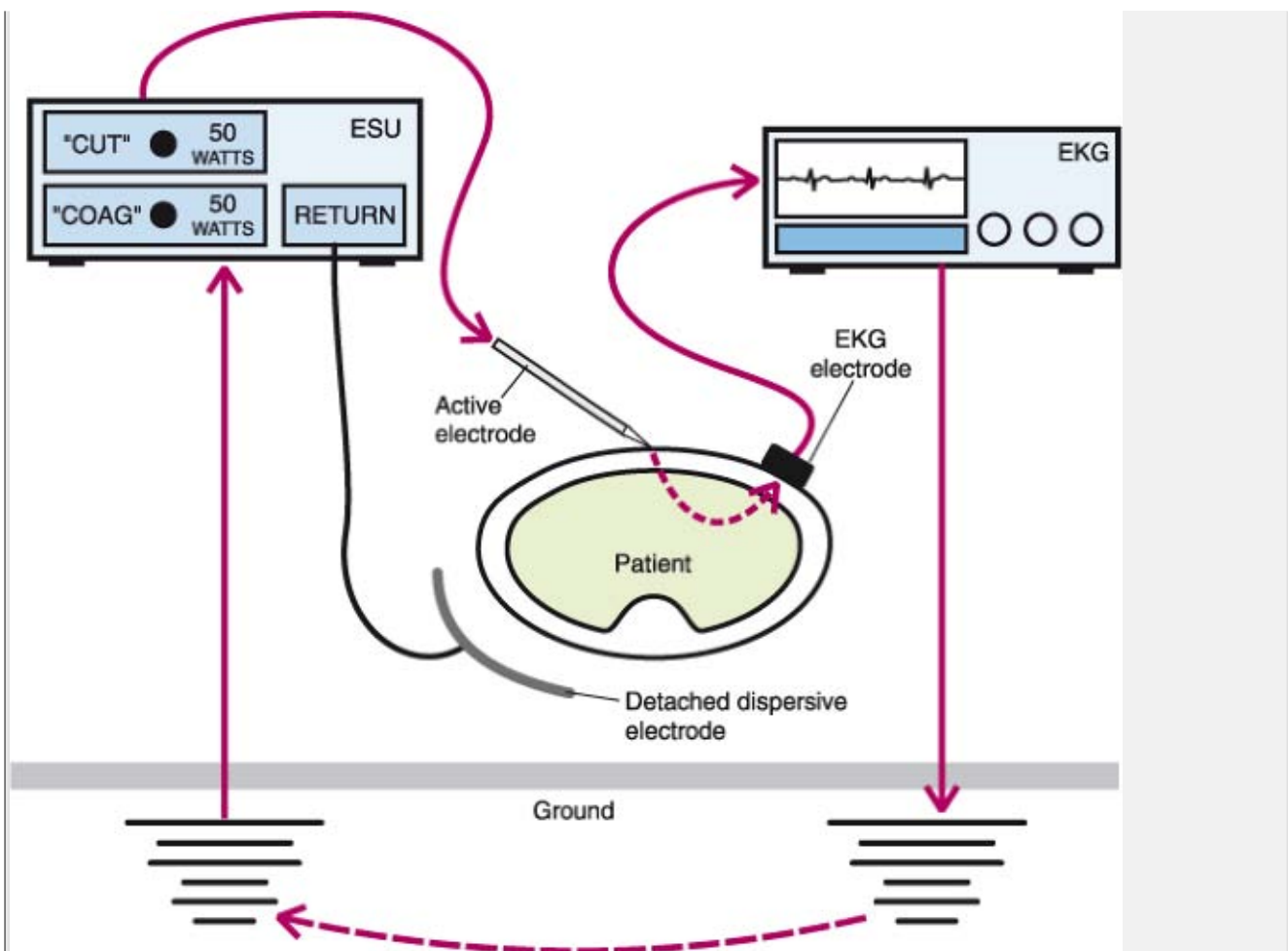


Figure 21.23 Risk of ground-referenced generators. Current diversion along alternate pathways is a risk associated with ground-referenced electrosurgical generators, particularly if the dispersive electrode is detached. In the example depicted, the relatively high current density at the electrocardiogram electrode site may result in a skin burn.



Distension Media →

Monitor →

Electric Exam Table

Camera Base

Light Source

Printer

Hysteroscopes,
Sheaths and
Camera Head

Video Recorder

Figure 21.24 Office Hysteroscopy Setup. Hysteroscopic procedures are facilitated with an electric examination table. Distension media may be positioned on an IV pole, but wide, cystoscopy tubing allows maintenance of higher intrauterine pressures suitable for viewing and performing simple procedures such as polypectomy or transcervical sterilization. A light source is necessary and a camera desirable. The camera is attached to the monitor and may be connected to a printer and/or video recorder. The camera head is attached to a flexible hysteroscope.

Hemorrhagic Complications

Great Vessel Injury

The most dangerous hemorrhagic complications are injuries to the great vessels, including the aorta and the vena cava, the common iliac vessels and their branches,

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and the internal and external iliac arteries and veins. The most catastrophic injuries occur secondary to insertion of an insufflation needle or the tip of the trocars used to position the primary or ancillary cannulas. The vessels most frequently damaged are the aorta and the right common iliac artery as it branches from the aorta in the midline. The anatomically more posterior location of the vena cava and the iliac veins provides relative protection, but not immunity, from injury (79). After vascular injury, patients usually develop profound hypotension with or without hemoperitoneum. In some instances, blood is aspirated through the insufflation needle before the introduction of the distending gas. **In such instances, the needle should be left in place while immediate preparations are made to obtain blood products and perform laparotomy.** The bleeding frequently will be contained in the retroperitoneal space, which usually delays the diagnosis; consequently, hypovolemic shock may develop. To avoid late recognition, the course of each great vessel must be identified before completing the procedure. Because it is difficult to assess the volume of blood filling the retroperitoneal space, immediate laparotomy is indicated if retroperitoneal bleeding is suspected. A midline incision should be made to allow access to the great vessels. Upon entry into the peritoneal cavity, the aorta and vena cava should immediately be compressed just below the level of the renal vessels to gain at least temporary control of blood loss. The most appropriate course of action depends on the site and extent of injury. Vascular or general surgery consultation may be necessary to evaluate and repair significant vascular injuries. Although most of these injuries are small and amenable to repair with suture, some are larger and require the insertion of a vascular graft. Deaths have occurred as a result of these injuries.

Abdominal Wall Vessel Injury

The abdominal wall vessels most commonly injured during laparoscopy are the superficial inferior epigastric vessels as they branch from the femoral artery and vein and course cephalad in each lower quadrant. They are invariably damaged by the initial passage of an ancillary trocar or by the introduction of a wider device later in the procedure. The problem may be recognized immediately by the observation of blood dripping along the cannula or out through the incision. However, the bleeding may be obstructed by the cannula until it is withdrawn at the end of the operation.

The more serious injuries are those to the deep inferior epigastric vessels, which are branches of the external iliac artery and vein that course cephalad but are deep to the rectus fascia and often deep to the muscles (Fig. 21.3). More laterally located are the deep circumflex iliac vessels, which are not often encountered in laparoscopic surgery. Laceration of these vessels may cause profound blood loss, particularly when the trauma is unrecognized and causes extraperitoneal bleeding.

Signs of injury, in addition to blood dripping down the cannula, include the postoperative appearance of shock and abdominal wall discolorization or hematoma located near the incision. In some instances, the blood may track to a more distant site, presenting as a pararectal or vulvar mass. Delayed diagnosis may be prevented

by laparoscopic evaluation of each peritoneal incision after removal of the cannula.

Superficial inferior epigastric vessel trauma usually stops bleeding spontaneously; therefore, expectant management is appropriate. A straight ligature carrier can be used to repair lacerated deep inferior epigastric vessels. Alternatively, a Foley catheter may be inserted through the cannula, inflated, put on traction, and held in place with a clamp for 24 hours. If a postoperative hematoma develops, local compression should be used initially. Open removal or aspiration of the hematoma should not be undertaken because it may inhibit the tamponade effect and increase the risk of abscess. However, if the mass continues to enlarge or if signs of hypovolemia develop, the wound must be explored.

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Intraperitoneal Vessel Injury

Hemorrhage may result from inadvertent entry into a vessel or failure of a specific occlusive technique. In addition to delayed hemorrhage, there may be a further delay in diagnosis at laparoscopy as a result of the restricted visual field and the temporary occlusive pressure exerted by CO₂ in the peritoneal cavity.

Inadvertent division of an artery or vein is usually evident immediately. **Transected arteries may go into spasm and bleed minutes to hours later, going unnoticed temporarily because of the limited visual field of the laparoscope. Therefore, at the end of the procedure, all areas of dissection must be carefully examined.** Carbon dioxide should be vented, which decreases the intraperitoneal pressure so that blood vessels temporarily occluded by higher pressure can be recognized.

Gastrointestinal Complications

The stomach, the small bowel, and the colon can be injured during laparoscopy. Mechanical entry into the large or small bowel can occur 10 times more often when laparoscopy is performed in patients who have had prior intraperitoneal inflammation or abdominal surgery. Loops of intestine can adhere to the abdominal wall under the insertion site and be injured (80,81).

Insufflation Needle Injuries

Needle entry into the gastrointestinal tract may be more common than reported because it often occurs unnoticed and without further complication. Gastric entry may be identified by the increased filling pressure, asymmetric distention of the peritoneal cavity, or aspiration of gastric particulate matter through the lumen of the needle. Initially, the hollow, capacious stomach may allow the insufflation pressure to remain normal. Signs of bowel entry are the same as those for gastric injury, with the addition of feculent odor.

If particulate debris is identified, the needle should be left in place, and an alternate insertion site should be identified, such as the left upper quadrant. Immediately after successful entry into the peritoneal cavity, the site of injury can be identified. Defects must be repaired immediately by laparoscopy or laparotomy.

Trocar Injuries

Damage caused by a sharp trocar is usually more serious than needle injury. Inadvertent gastric entry usually results from stomach distention because of aerophagia, difficult or improper intubation, or mask induction with inhalation anesthetic. Most often, the injury is created by the primary trocar. Ancillary cannulas may also result in visceral injury,

although placement of these cannulas under direct vision helps to reduce the risk of injury. **The risk of gastric perforation can be minimized with the selective use of preoperative nasogastric or oral gastric suction when left upper-quadrant entries are used or when the intubation was difficult.** Open laparoscopy likely has little impact on the risk for gastrointestinal complications, particularly those related to adhesions to the anterior abdominal wall from previous surgery. For high-risk patients, left upper quadrant needle and trocar insertion with a properly decompressed stomach may be preferable (82,83,84).

If the trocar of a primary cannula penetrates the bowel, the condition is usually diagnosed when the mucosal lining of the gastrointestinal tract is visualized. If the large bowel is entered, a feculent odor may be noted. However, the injury may not be immediately recognized because the cannula may not stay within the bowel or may pass through the lumen. Such injuries usually occur when a single loop of bowel is adherent to the anterior abdominal wall. The injury may not be recognized until peritonitis, abscess,

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enterocutaneous fistula, or death occurs (85,86). Therefore, at the end of the procedure, the removal of the primary cannula must be viewed either through the cannula or an ancillary port, a process facilitated by routine direct visualization of closure of the incision of the primary port.

Trocar injuries to the stomach and bowel require repair as soon as they are recognized.

If the injury is small, a trained operator can repair the defect by laparoscopy using a double layer of running 2-0 or 3-0 absorbable sutures. Extensive lesions may require resection and reanastomosis, which in most instances requires laparotomy. The preoperative use of mechanical bowel preparation in selected high-risk cases minimizes the need for laparotomy or colostomy.

Dissection and Thermal Injury

When mechanical bowel trauma is recognized during the dissection, treatment is the same as that described for trocar injury. **Should the injury involve radiofrequency electrical energy, it is important to recognize that the zone of desiccation may exceed the area of visual damage.** This is especially true if the exact mechanism of the thermal injury is unknown or if injury results from contact with a relatively large surface area electrode that would be more likely to create a large coagulation injury. Conversely, **bowel injury created under direct vision with a radiofrequency needle or blade electrode is associated with little collateral coagulation effect and, therefore, can be managed similar to a mechanically induced lesion.** Consequently, surgical repair should be implemented considering these factors, and should include, if necessary, resection of ample margins around the injury. **Thermal injury may be handled expectantly if the lesion seems superficial and confined,** such as is the case when fulguration (noncontact arcing of high-voltage current) involves bowel. In such instances, the depth of injury is generally less than half a millimeter. In a study of 33 women with such injuries who were managed expectantly in the hospital, only 2 required laparotomy for repair of perforation (87).

Urologic Injury

Damage to the bladder or ureter may occur secondary to mechanical or thermal trauma during laparoscopic procedures. Ideally, such injury should be prevented; otherwise, as is the case for most complications, it is preferable to identify the trauma intraoperatively.

Bladder Injury

Bladder injury can result from the perforation of the undrained bladder by a trocar, but it also

may occur while the bladder is being dissected from adherent structures or from the anterior uterus (88,89). The injury may be readily apparent by direct visualization. If an indwelling catheter is in place, hematuria or pneumaturia (CO₂ in the catheter drainage system) may be noticed. A bladder laceration can be confirmed by injecting sterile milk or a diluted methylene blue solution through a transurethral catheter. Thermal injury to the bladder, however, may not be apparent initially and, if missed, can present as peritonitis or a fistula.

Routine preoperative bladder drainage usually prevents trocar-related cystotomies. Separation of the bladder from the uterus or other adherent structures requires good visualization, appropriate retraction, and excellent surgical technique. Sharp mechanical dissection is preferred, particularly when relatively dense adhesions are present.

Very small-caliber injuries to the bladder (1-2 mm) may be treated with bladder catheterization for 3 to 7 days. If repair is undertaken immediately, catheterization is unnecessary. **When a larger injury is identified, it can be repaired laparoscopically**

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(88,89,90). **If the laceration is near the trigone or involves the trigone, however, an open procedure should be used.** The mechanism of injury should be taken into consideration in making this evaluation because electrical injuries often extend beyond the visible limits of the apparent defect.

For small lesions, closure may be performed with layers of absorbable 2-0 to 3-0 sutures. If thermal injury occurred, the coagulated portion should be excised. Postoperative catheterization with either a transurethral or suprapubic catheter should be maintained for 2 to 5 days for small fundal lacerations and for 10 to 14 days for injuries to the trigone. Cystography should be considered before the urinary catheter is removed.

Ureteral Injury

The most common cause of ureteral injury during laparoscopy is electrosurgical trauma (76,91). However, ureteral injury also can occur after mechanical dissection including linear cutting and stapling devices (92,93). **Although intraoperative recognition of ureteral injury is possible, the diagnosis is usually delayed** (91). Ureteral lacerations may be confirmed intraoperatively visually or with the intravenous injection of indigo carmine. Thermal injury presents up to 14 days after surgery with fever, abdominal or flank pain, and peritonitis. Leukocytosis may be present, and intravenous pyelography shows extravasation of urine or urinoma. Mechanical obstruction from staples or a suture may be recognized intraoperatively by direct visualization. **Cystoscopy following the intravenous injection of indigo carmine may be used to confirm failure of the dye to pass through the ureter.** Abdominal ultrasound may be helpful, but a CT urogram can more precisely identify the site and degree of the obstruction. Unrecognized ureteral obstruction may present a few days to 1 week after surgery with flank pain and often fever (93).

Discharge or continuous incontinence is a delayed sign of ureterovaginal or vesicovaginal fistulas. **A bladder fistula can be confirmed by detecting dye on a tampon previously placed in the vagina after filling the bladder with methylene blue. With a ureterovaginal fistula, the methylene blue will not pass into the vagina, but it can be detected with the intravenous injection of indigo carmine.**

Knowledge of the course of the ureter through the pelvis is a prerequisite to reducing the risk of injury. The ureter can usually be seen through the peritoneum of the pelvic sidewall between the pelvic brim and the attachment of the broad ligament. Because of variation from one patient to another or the presence of disease, however, the location of the ureter can become obscured, making it necessary to enter the retroperitoneal space. The

techniques used for retroperitoneal dissection are also important factors in reducing the risk of ureteric injury. Blunt and sharp dissection with scissors is preferred, although hydrodissection can be used (94). The selective placement of ureteral stents may also be helpful in preventing injury.

Ureteral injury can be treated immediately if it is diagnosed intraoperatively.

Although limited damage may heal over a ureteral stent left in place for 10 to 21 days, repair is indicated in most patients. Although laparoscopic repair of ureteric lacerations and transections has been performed, most injuries require laparotomy (91,95).

When the diagnosis of ureteral injury is delayed, the bladder should be drained with a catheter. Incomplete or small obstructions or lacerations may be treated successfully with either a retrograde or antegrade ureteral stent. Urinomas may be drained percutaneously. If a stent cannot be placed successfully, a percutaneous nephrostomy should be performed before operative repair is undertaken.

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Neurologic Injury

Peripheral nerve injury is usually related either to poor positioning of the patient or to excessive pressure exerted by the surgeons. Nerve injury may also occur as a result of the surgical dissection.

In the extremities, the trauma may be direct, such as when the common peroneal nerve is compressed against the stirrups. **The femoral nerve or the sciatic nerve or its branches may be overstretched and damaged by excessive flexion or external rotation of the hips. The peroneal nerve may be injured by compression if the lateral head of the fibula rests against the stirrups (96,97,98). Brachial plexus injuries may occur secondary to the surgeon or assistants leaning against the abducted arm during the procedure.** If the patient is placed in a steep Trendelenburg position, the brachial plexus may be damaged because of the pressure exerted on the shoulder joint. In most cases, sensory or motor deficits are found as the patient emerges from anesthesia. The likelihood of brachial plexus injury can be reduced with adequate padding and support of the arms and shoulders or by placing the patient's arms in an adducted position.

Most injuries to peripheral nerves resolve spontaneously. The time to recovery depends on the site and severity of the lesion. For most peripheral injuries, full sensory nerve recovery occurs in 3 to 6 months. Recovery may be hastened by the use of physical therapy, appropriate braces, and electrical stimulation of the affected muscles. Open microsurgery should be performed for transection of major intrapelvic nerves.

Incisional Hernia and Wound Dehiscence

Incisional hernia after laparoscopy has been reported in more than 900 cases (66,99). The most common defect is dehiscence that develops in the immediate postoperative period. Hernias may be asymptomatic or may cause pain, fever, periumbilical mass, obvious evisceration, and the symptoms and signs of mechanical bowel obstruction. **Although no incision is immune to the risk, defects that are larger than 10 mm in diameter are particularly vulnerable (99,100,101).**

Richter's hernias contain only a portion of the intestine in the defect, and the diagnosis is often delayed because the typical symptoms and findings of mechanical bowel obstruction may be absent. The initial symptom is usually pain. These hernias most often occur in incisions lateral to the midline where there is a greater amount of preperitoneal fat creating a potential space for incarceration. Fever can be present if incarceration occurs, and peritonitis may result

from subsequent perforation. The condition is difficult to diagnose, requires a high index of suspicion, and may be confirmed with ultrasonography or computed tomography (102).

In most cases, these occurrences can be prevented by using small-caliber cannulas, where possible, and with routine fascial and peritoneal closure of defects made by peritoneal access. The risk of inadvertent incorporation of the intestine into the wound can be reduced by viewing the closure with the laparoscope. A small-diameter laparoscope should be used through a narrow cannula to facilitate incisional closure. All ancillary cannulas should be removed under direct vision to ensure that bowel is not drawn into the incision and that no active bleeding is present in the incision.

The management of laparoscopic incisional defects depends on the time of presentation and the presence and condition of entrapped bowel. Evisceration always requires surgical intervention. If the condition is diagnosed immediately, the intestine is replaced into the peritoneal cavity (if there is no evidence of necrosis or intestinal defect), and the incision is repaired, usually with laparoscopic guidance. If the diagnosis is delayed or the bowel is incarcerated or at risk of perforation, laparotomy is necessary to repair or resect the intestine.

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Infection

Wound infections after laparoscopy are uncommon; most are minor skin infections that can be treated successfully with expectant management, drainage, or antibiotics (103). Severe necrotizing fasciitis can occur rarely (103). Bladder infection, pelvic cellulitis, and pelvic abscess have been reported (104).

Laparoscopy is associated with a much lower risk of infection than open abdominal or vaginal surgery. Prophylactic antibiotics should be offered to selected patients (e.g., those with enhanced risk for bacterial endocarditis and those for whom hysterectomy is planned). Patients should be instructed to monitor their body temperature after discharge and to report immediately a temperature higher than 38°C.

Hysteroscopy

The hysteroscope can be used to aid diagnosis or to direct the performance of a variety of intrauterine procedures. Hysteroscopic lysis of intrauterine adhesions was first described in 1973 (105). The technique of endoscopically guided electrosurgical resection was adapted from urology to gynecology for the removal of uterine leiomyomas (106). Hysteroscopic division of uterine septa was originally developed using a mechanical technique with specially designed scissors (107). Hysteroscopic destruction of the endometrium has been reported using Nd:YAG laser vaporization, and using electrosurgical desiccation or resection, and vaporization. More recently, hysteroscopically guided thermal ablation with heated fluid has been described (108,109,110).

Developments in the design of endoscopes have resulted in smaller-diameter instruments that retain the ability to provide a high-quality image. Such developments further facilitate the use of hysteroscopy in an office or procedure room setting.

Diagnostic Hysteroscopy

The goal of evaluation of the uterine cavity is either to obtain a sample of the endometrium, usually for the detection of hyperplasia or neoplasia, or to identify structural abnormalities such as polyps, myomas, or a uterine septum.

Blind endometrial sampling has been the diagnostic mainstay for the detection of endometrial hyperplasia, whereas transvaginal ultrasonography, hystero­graphy, and hysteroscopy are options in the detection and characterization of structural anomalies. **Hysteroscopic examination is probably superior to hystero­graphy in the evaluation of the endometrial cavity (111,112), but the diagnostic accuracy of transvaginal ultrasonography is similar, especially when intrauterine saline is used as a contrast medium, a procedure called sonohystero­graphy or saline infusion sonography (SIS) (113).** Ultrasound-based techniques have the advantage of allowing evaluation of the myometrium, whereas office-based hysteroscopy allows simultaneous removal of small polyps and even some myomas. Diagnostic hysteroscopy provides information not obtained by blind endometrial sampling (114,115,116,117,118,119,120), such as detection of endometrial polyps or submucous leiomyomas (117,118,120,121). Malignant or hyperplastic polyps or other localized lesions can be identified with hysteroscopy and removed via directed biopsy (119). However, blind curettage remains an effective approach for the identification of endometrial histopathology (115,118,120,122). **Following are potential indications for diagnostic hysteroscopy.**

- Unexplained abnormal uterine bleeding
 - Premenopausal
 - Postmenopausal

- Selected infertility cases
 - Abnormal hystero­graphy or transvaginal ultrasonography
 - Unexplained infertility
- Recurrent spontaneous abortion

For most patients, diagnostic hysteroscopy can be performed in an office or clinic with minimal discomfort and at a much lower cost than in an operating room. For some, concerns about patient comfort or a pre-existing medical condition may preclude office hysteroscopy. Although hysteroscopy can, in many patients, provide more information than blind curettage, it should still be used prudently. For most patients, other diagnostic or therapeutic measures can be undertaken before, or instead of, diagnostic hysteroscopy. For example, in women with perimenopausal and postmenopausal bleeding, office endometrial biopsy or curettage should be the initial method of assessment. If a satisfactory diagnosis cannot be established, or if bleeding continues without explanation, further investigation with ultrasound, SIS, or office hysteroscopy is appropriate. For women in their reproductive years who have abnormal uterine bleeding, medical or expectant management may be used initially, depending on the severity and inconvenience of the bleeding. For those who do not respond to medical treatments such as oral contraceptives, transvaginal ultrasonography, SIS, or hysteroscopy with biopsy, if appropriate, can be performed

for diagnosis (123).

For women with infertility, hysterosalpingography is the best initial imaging step because it provides information about the patency of the oviducts. In the presence of a suspicious or identified abnormality in the endometrial cavity, hysteroscopy can be performed to confirm the diagnosis, to define the abnormality, and perhaps to direct the removal of the lesion. Some experts consider hysteroscopy mandatory for such patients because of the high occurrence of false-negative radiologic images in those with intrauterine anomalies. However, there has been no evidence that identification and treatment of these "missed" anomalies improves pregnancy rates. Confirmation of patency of the oviduct is unnecessary in women who have recurrent abortions; therefore, these patients can be evaluated primarily with hysteroscopy.

Operative Hysteroscopy

A number of intrauterine procedures can be performed under endoscopic direction, including adhesiolysis, sterilization, division of a uterine septum, resection of myomas, and endometrial destruction through Nd:YAG laser vaporization or radiofrequency resection, desiccation, or vaporization. Hysteroscopy may also be used to direct the removal of foreign bodies or to position occluding devices in the fallopian tube for sterilization.

Foreign Body

If the string of an intrauterine device is absent, the device usually can be removed with a specially designed hook or a toothed curette (e.g., Novak). When removal is difficult or impossible, the location of the device may be confirmed by hysteroscopy, allowing removal with a grasping forceps.

Septum

When recurrent pregnancy loss is associated with a single corpus containing a uterine septum, hysteroscopic division of the septum improves reproductive outcome at a rate comparable to abdominal metroplasty, with reduced morbidity and cost (see Chapter 31) (124,125,126,127,128). The procedure may be performed mechanically with scissors or with energy-based techniques such as the Nd:YAG laser or an electrosurgical knife or loop. Because most septa have few vessels, scissors can be used easily, and the minimal risk for thermal damage is avoided.

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Endometrial Polyps

Although endometrial polyps can be removed with blind curettage, many are missed (117,118,120,121). Therefore, known or suspected endometrial polyps are more successfully treated with hysteroscopic guidance, which can often be performed in a clinic or office using local anesthesia. Hysteroscopy may be used either to evaluate the result of blind curettage or use of grasping forceps, or preferably, with appropriate operating sheaths, to guide directed removal with small-caliber scissors or grasping forceps. Alternatively, for larger polyps, a uterine resectoscope may be used to sever the stalk or morcellate the lesion.

Leiomyomas

Hysteroscopy may be used to remove selected leiomyomas that involve the uterine cavity in women with heavy menstrual bleeding or infertility (113,129,130,131,132,133,134,135).

However, this approach is limited based on the location, size, and number of the lesions. Preoperative administration of gonadotropin-releasing hormone (GnRH) agonists may help shrink submucous myomas, facilitating their complete removal. Perhaps more importantly, they reduce operating time and systemic absorption of distension media (136,137,138).

To help document and evaluate the results of hysteroscopically directed myoma surgery, a classification system has been developed that is based on the proportion of the myoma that is in the uterine cavity. **In patients with myomas that are 5 cm or less in diameter and entirely intracavitary (Type 0), excision is feasible and in many instances relatively easy, whereas in large type 2 lesions an abdominal approach with laparoscopy or laparotomy will be necessary.** Small type 0 leiomyomas may be removed following transection of the stalk with scissors or an electrode attached to a uterine resectoscope. For larger type 0 lesions, or for type 1 myomas, electrosurgical morcellation with a resectoscope is necessary before removal. For a limited number of type 2 myomas, careful myometrial dissection may be attempted provided that ultrasonography or magnetic resonance imaging has demonstrated an adequate margin of myometrium between the deepest aspect of the lesion and the serosa. It may be preferable to undertake such procedures with laparoscopic monitoring to ensure that bowel is not adjacent to the zone of dissection. Patients should be counseled that for some type 1 and 2 myomas, it may take more than one procedure to complete excision (134). Alternatively, the Nd:YAG laser or radiofrequency electrodesiccation can be used to destroy the remaining portion of the leiomyoma, although the efficacy of this approach is unclear (130). The use of intrauterine prostaglandin F_{2α} has also been described to facilitate extrusion of type 2 myomas (139).

Endometrial Ablation

Heavy Menstrual Bleeding

Heavy menstrual bleeding that does not respond to oral medical therapy may be managed by endometrial ablation or resection, provided the patient is willing to forego future fertility (108,109,110,132,138,140,141,142,143,144,145,146,147).

Alternatively, or if future fertility is desired, a levonorgestrel—releasing intrauterine contraceptive device can provide virtually equal clinical outcomes (148,149). Ablation may be performed with the laser (108,139,140) by radiofrequency electrosurgical desiccation, resection, or vaporization using a uterine resectoscope (110,150) or by any of a number of nonresectoscopic techniques, including those employing thermal balloons, bipolar radiofrequency, cryonics, heated free fluid, or microwaves (151,152,153,154,155).

Endometrial resection is performed with an electrosurgical loop electrode that can shave the endometrium and superficial myometrium (109,142,143). Vaporization utilizes specially designed electrodes that are attached to standard resectoscopes but which are capable of removing large volumes of tissue without morcellation (156). Ablation is achieved using ball or barrel—shaped electrodes that coagulate the endometrial surface

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(110). Complications of these procedures include fluid overload, electrolyte imbalances (if nonelectrolytic media are used), uterine perforation, bleeding, and intestinal and urinary tract injury (140,145). The risk of uterine perforation may be reduced by using a combination of resection or vaporization and electrosurgical ablation; the latter is most suitable for the thinner areas of the myometrium in the cornu (132). The preoperative use of GnRH analogues or *danazol* may reduce operating time, and GnRH may reduce bleeding and the amount of fluid absorbed into the systemic circulation (157,158).

For many women, these procedures are successful in reducing or eliminating menses without hysterectomy or long-term medical therapy (129,159,160). Success rates vary and depend on the duration of follow-up and the definition of success. For many patients, amenorrhea is the goal, whereas for others, it is normalization of menses. About 75% to 95% of patients are satisfied with the surgical procedure after 1 year, and 30% to 90% of patients have amenorrhea. In comparative studies, there is no advantage of laser over electrosurgical techniques (140,145). The nonresectoscopic techniques have similar clinical outcomes, thus reducing the need for resectoscopic ablation. However, the nonresectoscopic approaches all have limitations defined by the size or configuration of the endometrial cavity. Consequently, for those women with heavy menstrual bleeding who are not suitable for nonresectoscopic techniques because of large uteri (>12 cm sounded length), resectoscopic endometrial ablation remains a viable option (161).

The long-term efficacy and impact of ablation or resection on women with adenomyosis is unknown. Because some endometrium inevitably cannot be ablated, there is the potential for endometrial cancer; therefore, postmenopausal women who have undergone ablation or resection should take progestin as a part of hormonal therapy (159).

Sterilization

Sterilization can be performed under hysteroscopic guidance, an approach that eliminates the disadvantages and risks associated with abdominal or laparoscopic techniques (162,163). One such technique is currently available, and others are currently under development. The Essure system comprises a nickel-titanium coil with a Dacron filament that can be inserted relatively quickly in an office or procedure room setting (see Chapter 10). Current protocols require that hysterosalpingography be performed 3 months after the procedure to ensure that bilateral tubal occlusion has taken place.

Synechiae

Asherman's syndrome is the presence of adhesions in the endometrial cavity resulting in infertility or recurrent spontaneous abortion with or without amenorrhea. These synechiae may be detected on a hystrogram but are best shown with diagnostic hysteroscopy. Relatively thin, fragile synechiae may be divided with the tip of a rigid diagnostic hysteroscope (164). Thicker lesions may require division by semirigid or rigid scissors or energy-based instruments such as a resectoscope or an operative hysteroscope with an Nd:YAG laser. Reproductive outcome depends on the extent of the preoperative endometrial damage (125,165,166).

Patient Preparation and Communication

Most diagnostic hysteroscopy procedures are performed in the office or clinic, whereas operative hysteroscopy is usually performed in an operating room or hospital surgicenter. The patient should understand the rationale for either procedure, as well as the anticipated discomfort, the potential risks, and the expectant, medical, and surgical alternatives. The nature of the procedure and the chance of therapeutic success should be explained to the patient, and she should be given a realistic estimate of success based on the operator's experience.

Diagnostic Hysteroscopy: Risks

The risks of diagnostic hysteroscopy are few, and those complications that occur rarely have severe consequences. However, those risks related to anesthesia, perforation, bleeding,

and the distention media should be discussed. After diagnostic hysteroscopy, most patients have slight vaginal bleeding and occasionally, lower abdominal cramps. Severe cramps, dyspnea, and upper abdominal and right shoulder pain can develop if CO₂ passes into the peritoneal cavity. Consequently, the patient should be accompanied by a friend or relative to escort her home.

Operative Hysteroscopy: Risks

Counseling before operative hysteroscopy varies depending on the planned procedure and the type of anesthesia used. **The risks of operative hysteroscopy are higher and potentially more dangerous than those of diagnostic hysteroscopy.** These risks include those associated with anesthesia, intrinsic to all hysteroscopic procedures, and related to the specific surgical procedure to be performed. **With any hysteroscopic procedure, air embolus is a possibility, as are complications associated with the gaseous or fluid distention media used.** Hypotonic distention media may not be tolerated in some patients if there is significant intravascular absorption, especially in patients with underlying cardiovascular disease. The patient must also be aware of the risks associated with uterine perforation, which range from failure to complete the procedure to hemorrhage or damage to the intestines or to the urinary tract. If such complications occur, laparotomy may be necessary to repair the injury.

Equipment and Technique

The equipment required for hysteroscopy depends on the reason for the procedure. The surgeon must be knowledgeable about the equipment, its mechanisms, and the technical specifications to facilitate efficiency, optimal clinical outcome, and a decreased probability of complications. A typical hysteroscopy setup for diagnostic and minor operative procedures is shown in Figures 21.24 and 21.25. Core competencies required for hysteroscopy are as follows:

- Patient positioning and cervical exposure
- Anesthesia
- Cervical dilation
- Uterine distention
- Imaging
- Intrauterine manipulation

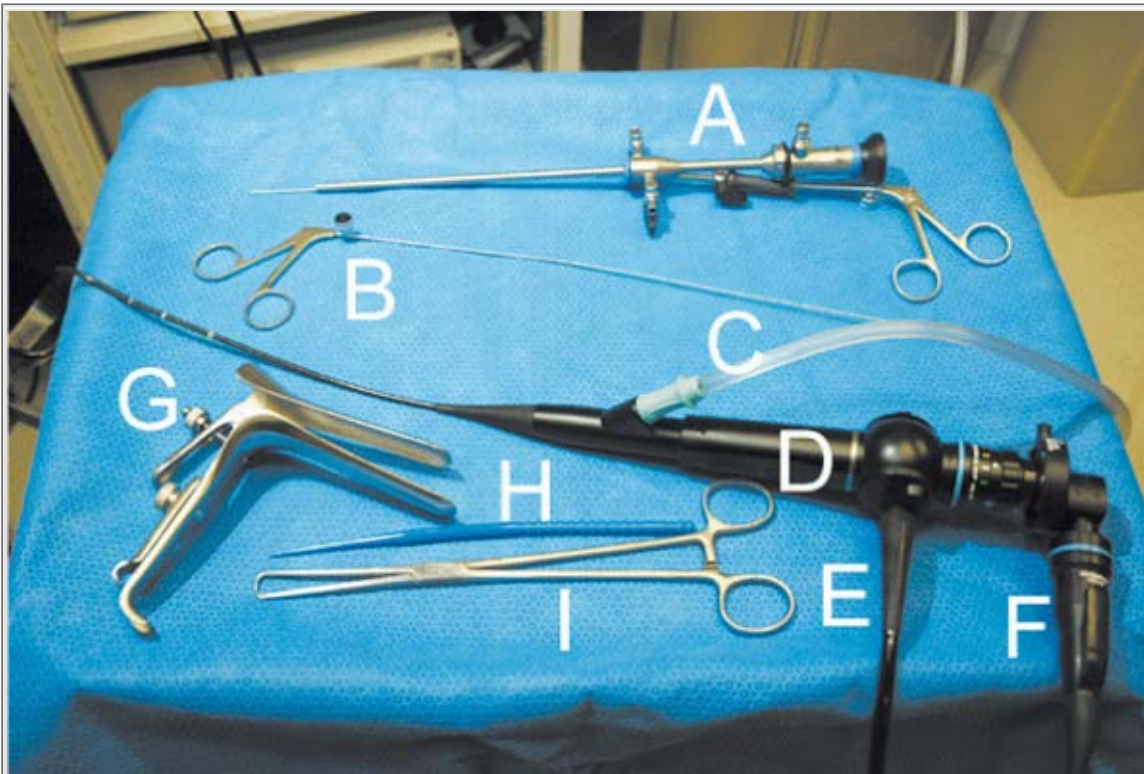


Figure 21.25 Office Hysteroscopy Instruments. An assembled continuous flow operating hysteroscope with a 5.5-mm diameter external sheath is shown in **A**. A 5 French semirigid scissors occupies the working channel. An additional biopsy forceps is shown in **B**. Tubing transporting media to the system is shown in **C** going into a 3-mm external diameter flexible and steerable hysteroscope (**D**). A medical video camera is attached to the hysteroscope (**F**) and the light source is attached at (**E**). An open speculum (**G**) facilitates removal with instruments in place. A small dilator (**H**) or series of dilators will be necessary for a large number of patients. A tenaculum (**I**) attached to the cervix frequently facilitates both dilation and entry of the hysteroscope into the endometrial cavity.

Patient Positioning and Exposure

Hysteroscopy is performed in a modified dorsal lithotomy position; the patient is supine, and the legs are held in stirrups. For hysteroscopic procedures performed while the patient is conscious, comfort must be considered in conjunction with the need to gain good exposure of the perineum. Stirrups that hold and support the knees, calves, and ankles permit prolonged procedures. "Candy cane" stirrups should be avoided for hysteroscopic surgery on conscious patients.

The smallest speculum possible should be used to expose the cervix. A bivalve speculum hinged on only one side allows its removal without disturbing the position of the tenaculum and hysteroscope. The use of weighted specula should be avoided in conscious patients because of the discomfort involved.

Anesthesia

The anesthetic requirements for hysteroscopy vary greatly, depending on the patient's level of anxiety, the status of her cervical canal, the procedure, and the outside diameter of the hysteroscope or sheath. **In some patients, diagnostic hysteroscopy is possible without**

anesthesia, especially if the patient is parous or if narrow—caliber (<3 mm in outside diameter) hysteroscopes and sheaths are used. The pain of cervical dilation also is avoided or minimized by inserting a laminaria tent in the cervix 3 to 8 hours before the procedure. However, if laminaria are left in place too long (e.g., longer than 24 hours), the cervix may overdilate, which is counterproductive for CO₂ insufflation.

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For most diagnostic procedures, effective cervical anesthesia is obtained with an intracervical block. A spinal needle can be used to instill about 3 mL of 0.5% to 1% lidocaine into the anterior lip of the cervix. A tenaculum is used to grasp the cervix. An intracervical block is administered evenly around the circumference of the internal os. A paracervical block may also be injected into the uterosacral ligaments at the 4- and 8-o'clock positions, if necessary (167). Care must be taken to avoid intravascular injection. Additional topical anesthesia may be given by injecting 5 mL of 2% *mepivacaine* into the endometrial cavity with a syringe. Many operative procedures can be performed with this technique combined with intravenous use of anxiolytics or analgesics, as necessary. Alternatively, regional or general anesthesia may be used.

Cervical Dilation

Dilation of the cervix, although apparently simple, can be incorrectly performed in a way that compromises the whole procedure. If the objective lens of the hysteroscope cannot be placed in the endometrial cavity, the hysteroscopy cannot be done. Although findings have been inconsistent, preoperative administration of prostaglandin E₁ (*misoprostol*) to ripen the cervix 12 hours before the procedure (400 µg orally or 200 µg vaginally) may facilitate cervical dilation (168,169). Alternatively, there is evidence that intracervical injection of *vasopressin* (0.05 U/mL, 4 cc at 4 and 8 o'clock) also substantially reduces the force required for cervical dilation (170). The cervix should be dilated as atraumatically as possible. It is best to avoid using a uterine sound because it can traumatize the canal or the endometrium, causing unnecessary bleeding and uterine perforation.

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Uterine Distention

Distention of the endometrial cavity is necessary to create a viewing space. The choices include CO₂ gas, high-viscosity 32% *dextran 70*, and a number of low-viscosity fluids, including glycine, sorbitol, saline, and dextrose in water. **A pressure of 45 mm Hg or higher is generally required for adequate distention of the uterine cavity. To minimize extravasation, this pressure should not exceed the mean arterial pressure.** For each of the fluids, there are several methods used to create this pressure by infusion into the endometrial cavity.

Sheaths

A rigid hysteroscope is passed into the endometrial cavity through an external sheath. The design and diameter of the sheath reflect both the dimensions of the endoscope and the purpose of the instrument. Diagnostic hysteroscopes have a sheath slightly wider than the telescope, allowing infusion of the distention media. Sheaths for operative hysteroscopes have one or two additional channels that permit the passage or efflux of distention media or the insertion of semirigid instruments or laser fibers. These sheaths are usually 5 to 8 mm in

diameter, and some allow continuous flow of distention media in and out of the endometrial cavity (Figs. 21.25,21.26).

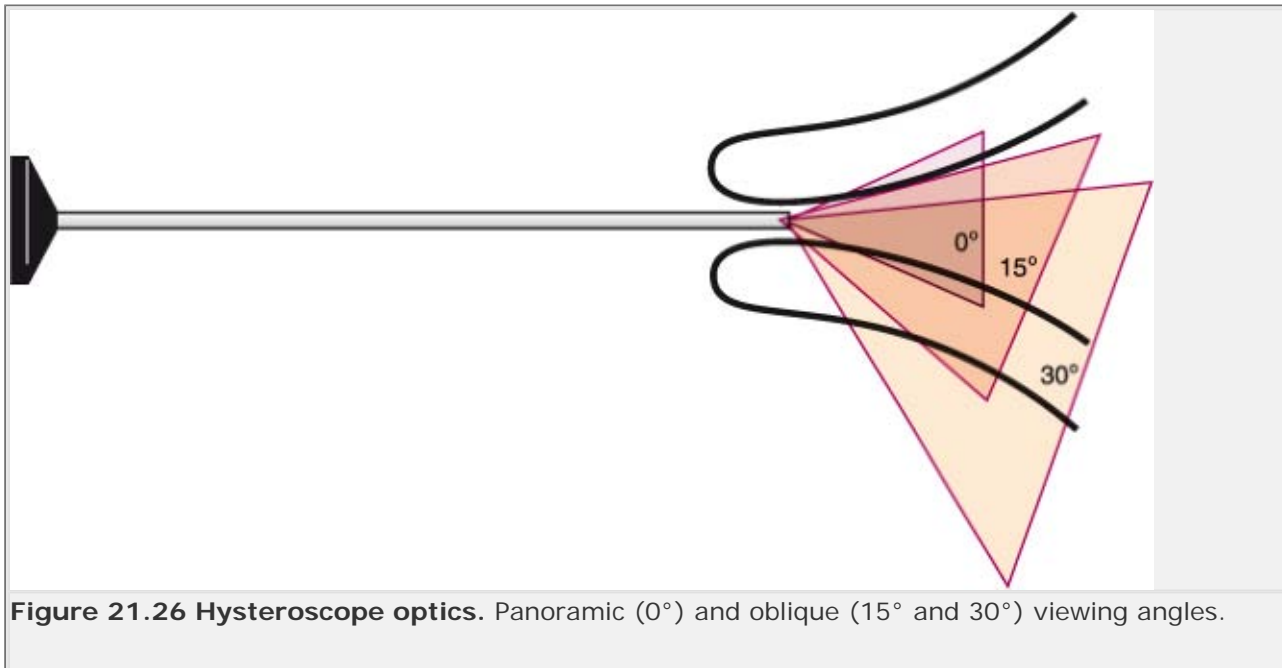


Figure 21.26 Hysteroscope optics. Panoramic (0°) and oblique (15° and 30°) viewing angles.

Media

CO₂ provides an excellent view for diagnostic purposes, but it is unsuitable for operative hysteroscopy and for diagnostic procedures when the patient is bleeding because there is no effective way to remove blood and other debris from the endometrial cavity. To prevent CO₂ embolus, the gas must be instilled by an insufflator that is specially designed for the procedure—the intrauterine pressure is kept below 100 mm Hg, and the flow rate is maintained at less than 100 mL/min.

Normal saline is a useful and safe medium for procedures that do not require radiofrequency electricity from standard monopolar resectoscopes. Even if there is absorption of a substantial volume of solution, saline does not cause electrolyte imbalance. Therefore, saline is a good fluid for minor procedures performed in the office. The development of bipolar radiofrequency instrumentation for hysteroscopic surgery has allowed the application of saline as a distending medium in even more advanced and complex procedures.

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Dextran 70 is useful for patients who are bleeding, because it does not mix with blood. However, it is expensive and tends to “caramelize” on instruments, which must be disassembled and thoroughly cleaned in warm water immediately after each use. Anaphylactic reactions, fluid overload, and electrolyte disturbances can occur.

For standard operative hysteroscopy with monopolar radiofrequency resectoscopes, low-viscosity, nonconductive fluids such as 1.5% glycine, 3% sorbitol, and 5.0% mannitol are used most often. These solutions can be used with standard, monopolar radiofrequency instrumentation because there are no electrolytes to disperse the current and impede the electrosurgical effect. Each of these media is inexpensive and readily available, usually in 3-L bags suitable for continuous-flow hysteroscopy. Because each fluid is electrolyte-free, extravasation into the systemic circulation can be associated with electrolyte disturbances. Compared with 1.5% glycine or 3.0% sorbitol,

5% mannitol is isosmolar, and it functions as a diuretic, both advantages when performing resectoscopic surgery. **Regardless of the electrolyte content of the fluid distending media, systemic "absorption" must be monitored continuously or at least frequently (every 5 minutes) by collecting outflow from the sheath and subtracting it from the total infused volume.** There exist a number of machines designed to provide continuous feedback to the surgeon regarding the degree of negative fluid balance. Absorbed volumes greater than 1L mandate the measurement of electrolyte levels. The administration of an appropriate dose of furosemide should be considered, and the surgeon should plan for the expeditious completion of the procedure. If there is more than a preset limit (1.5–2 L of extravasated fluid), the procedure should be stopped. Excessive circulating sorbitol may cause hyperglycemia, and large volumes of glycine may elevate levels of ammonia in the blood (171).

Media Delivery Systems

Syringes can be used for office diagnostic procedures and are especially good for infusing *dextran* solution. The syringe can be operated by the surgeon and is either connected directly to the sheath or attached by connecting tubing. Because this technique is so tedious, it is suited only for simple operations.

Continuous hydrostatic pressure is effectively achieved by elevating the vehicle containing the distention media above the level of the patient's uterus. The achieved pressure is the product of the width of the connecting tubing and the elevation—for operative hysteroscopy with 10–mm tubing, intrauterine pressure ranges from 70 to 100 mm Hg when the bag is between 1 to 1.5 m above the uterine cavity.

A pressure cuff may be placed around the infusion bag to elevate the pressure in the system. Caution must be exercised, however, because this technique causes increasing extravasation if intrauterine pressure rises above the mean arterial pressure.

A variety of infusion pumps are available, ranging from simple devices to instruments that maintain a preset intrauterine pressure. Simple pump devices continue to press fluid into the uterine cavity regardless of resistance, whereas the pressure-sensitive pumps reduce the flow rate when the preset level is reached, thereby impeding the efflux of blood and debris and compromising the view.

Imaging

Endoscopes

Hysteroscopes are available in two basic types—flexible and rigid. Flexible hysteroscopes have lower resolution than rigid instruments of a similar diameter and are most useful for cannulation of the fallopian tube. For other uses, rigid hysteroscopes are more durable and provide a superior image. The most commonly used hysteroscopes are 3 to 4 mm in

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diameter, although those smaller than 2 mm in diameter are available. Small-diameter endoscopes have a somewhat lower resolution but are easier to pass through the cervix.

Endoscopes with angled (foreoblique) lenses are useful for hysteroscopy and are available in 0-degree, 12- to 15-degree, and 25- to 30-degree models (Fig. 21.26). The 0-degree telescope provides a panoramic view and is best for diagnostic procedures. Hysteroscopes with 25- to 30-degree angles are most often used for cannulation of the fallopian tubes or placement of sterilization devices, whereas 12- to 15-degree designs are a suitable compromise useful

for diagnosis and ablation or resection.

Light Sources and Cables

Adequate illumination of the endometrial cavity is essential. Because it runs from a standard 110- or 220-volt wall outlet, the light source requires no special electrical connections. For most cameras and endoscopes, the element must have at least 150 watts of power for direct viewing and preferably 250 watts or more for video and operative procedures (172).

Video Imaging

Although diagnostic hysteroscopy may be performed with direct visualization, it is best to use video guidance for prolonged operations. Video imaging is important for teaching and recording pathology and procedures. The camera must be sensitive because of the narrow diameter of the endoscope and the frequently dark background of the endometrial cavity, particularly when it is enlarged (Fig. 21.25).

Image Documentation

A small video camera can be used to teach and to coordinate the procedure with the operating room team. It also allows the acquisition of still or video images for future reference or teaching. When a video recorder is used, the camera should be attached directly to the recorder to preserve the image quality. A number of video recording formats are available, each with inherent advantages and disadvantages. Some video printers provide images suitable for a medical record. Newer digital cameras provide video still images, slides, or prints that are suitable for publication or teaching.

Intrauterine Surgery

The instruments available for use through operative hysteroscopes include grasping, cutting, and punch-biopsy devices. These tools are narrow and flexible enough to navigate the 1- to 2-mm diameter operating channel (Fig. 21.25). Their value is limited by their small size and flimsy construction; however, the scissors can be used to divide adhesions, the biopsy forceps can be used to sample targeted lesions, and the grasping forceps can be used to remove small polyps or intrauterine devices. Some operative hysteroscopes are designed to allow passage of fibers for the conduction of Nd:YAG laser.

The uterine resectoscope is similar to the one used in urology and is designed to apply radiofrequency electrical energy in the endometrial cavity (Fig. 21.27). An understanding of the principles of electrosurgery is mandatory for safe and effective use of this instrument. By sliding the "working element," one of a variety of electrode tips can be manipulated back and forth within the cavity. Tissue can be divided with a pointed electrode, excised with a loop, or desiccated with a rolling ball or bar. An electrode with multiple tips or edges can be used to vaporize tissue, provided high generator outputs are used. A clear operative field is maintained by the continuous flow of nonconductive distending media in and out of the cavity. Although basic design modifications have made the resectoscope more useful in gynecology, extraction of resected fragments is time consuming. The most effective approach is the periodic use of a uterine curette or polyp forceps inserted after

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removal of the hysteroscope. Alternatively, much of the myoma or endometrium can be vaporized, thereby minimizing the need for periodic but time-consuming removal of tissue "chips." If vaporization is used, it is still important to obtain representative samples of the endometrium

or myoma for pathological analysis.



Figure 21.27 Resectoscope. The assembled resectoscope is shown, with two electrodes in the foreground. Manipulation of the electrode is via the white handle in the proximal portion of the device.

Other Instruments

For any hysteroscopic procedure, it is necessary to have available a cervical tenaculum, dilators, uterine curette, and appropriate-sized vaginal specula. When using the resecto scope, it is helpful to have a modern, solid-state, isolated circuit electrosurgical generator capable of delivering both modulated and nonmodulated radiofrequency current. Laparoscopy or laparotomy may be necessary for emergencies secondary to uterine perforation.

Complications

The potential risks of diagnostic hysteroscopy include uterine perforation, infection, excessive bleeding, and complications related to the distention media (145). The latter include CO₂ embolus and pulmonary edema secondary to overinfusion of 32% *dextran 70* (*Hyskon*) or low-viscosity fluids. Diagnostic hysteroscopy performed in the office has a low rate of complications (0%–1%) (114,115,116). **The risks of operative hysteroscopy are related to one of five aspects of the procedure performed: (i) anesthesia, (ii) the distention media, (iii) perforation, (iv) bleeding, and (v) the use of energy.**

Anesthesia

Local anesthesia is provided by the intracervical or paracervical injection of 0.5% to 2% *lidocaine* or *mepivacaine* solution, with or without a local vasoconstrictor such as adrenaline. Overdosage is prevented by ensuring that intravascular injection is avoided and by not exceeding the maximum recommended doses (*lidocaine*, 4 mg/kg; *mepivacaine*, 3 mg/kg). The use of a vasoconstrictor reduces the amount of systemic absorption of the agent, doubling the maximum dose that can be used.

Complications of intravascular injection or anesthetic overdose include allergy, neurologic effects, and impaired myocardial conduction. Allergy is characterized by the typical symptoms of agitation, palpitations, pruritus, coughing, shortness of breath, urticaria, bronchospasm, shock, and convulsions. Treatment measures include administration of oxygen, isotonic intravenous fluids, intramuscular or subcutaneous adrenaline, and intravenous prednisolone

and aminophylline. Cardiac effects related to impaired myocardial conduction include bradycardia, cardiac arrest, shock, and convulsions. Emergency treatment measures

include the administration of oxygen, intravenous *atropine* (0.5 mg), and intravenous *adrenaline*, and the initiation of appropriate cardiac resuscitation. The most common central nervous system manifestations are paresthesia of the tongue, drowsiness, tremor, and convulsions. Options for therapy include intravenous *diazepam* and respiratory support.

Distention Media

Carbon Dioxide

Carbon dioxide is highly soluble in blood; consequently, even if emboli occur, they are rarely clinically significant. However, rarely, CO₂ emboli may result in

serious intraoperative morbidity and even death (173,174,175). These risks can be eliminated by not using CO₂ with operative procedures, and by ensuring that the insufflation pressure is always lower than 100 mm Hg and that the flow rate is lower than 100 mL/min. The insufflator used must be especially designed for hysteroscopy; it is difficult to set laparoscopic insufflator flow rates below 1,000 mL/min.

Dextran 70

Dextran 70 is a hyperosmolar medium that can induce an allergic response, coagulopathy, and, if sufficient volumes are infused, vascular overload and heart failure (176,177). Because dextran is hydrophilic, it can draw 6 times its own volume into the systemic circulation. Consequently, the volume of this agent should be limited to less than 300 mL, particularly for office use.

Low-Viscosity Fluids

The low-viscosity fluids—1.5% glycine, 3% sorbitol, and 5.0% mannitol—are most often used, largely because of their low cost, compatibility with standard electrosurgery, and availability in large-volume bags. However, the use of a continuous-flow system with hypotonic media can create fluid and electrolyte disturbances.

- **Before undertaking a procedure using the resectoscope, baseline serum electrolyte levels should be measured.** Women with cardiopulmonary disease should be evaluated carefully. The selective preoperative use of agents such as GnRH agonists may reduce operating time and media absorption. Intracervical injection of 8 mL dilute intracervical vasopressin (0.01 U/mL) has been shown effective at reducing the amount of systemic absorption of distending media (178).

- **In the operating room, media infusion and collection should take place in a closed system to allow accurate measurement of the “absorbed” volume.** The volume should be measured continuously with a device specifically designed for the purpose or calculated every 5 to 10 minutes.

- **The lowest intrauterine pressure necessary for adequate distention should be used to complete the operation, usually at a level that is below the mean arterial pressure.**

A good range is 70 to 80 mm Hg, which can be achieved with a specially designed pump or by maintaining the meniscus of the infusion bag 1 m above the level of the patient's uterus.

Deficits of more than 1 L require measurement of electrolyte levels and may require an appropriate dose of intravenous furosemide. The procedure should be completed expeditiously. If the deficit is more than a preset limit (1.5–2 L), the procedure should be terminated, and a diuretic such as *mannitol* or *furosemide* should be used as needed. In patients with cardiovascular compromise, deficits must be avoided (179).

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Perforation

Perforation may occur during dilation of the cervix or during the hysteroscopic procedure. With perforation, the endometrial cavity does not distend, and the visual field is lost.

When perforation occurs during dilation of the cervix, the procedure must be terminated, but usually there are no other injuries. If the uterus is perforated by a hysteroscopic instrument, the tip of a laser, or an activated electrode, there is a risk for bleeding or injury to the adjacent viscera. Therefore, the operation must be stopped and the instruments withdrawn under hysteroscopic guidance.

If there is evidence of bleeding or presumed visceral injury, laparoscopy or laparotomy should be performed. Injury to the uterus is relatively easy to detect with a laparoscope. However, mechanical or thermal injury to the bowel, ureter, or bladder is more difficult and may require laparotomy. If the patient's condition is managed expectantly, she should be advised of the situation and asked to report any symptoms of bleeding or visceral trauma such as fever, increasing pain, nausea, and vomiting.

Bleeding

Bleeding that occurs during or after hysteroscopy results from trauma to the vessels in the myometrium or injury to other vessels in the pelvis. Myometrial vessels can be lacerated during the resectoscopic procedures.

In planning operations that involve deep resection, autologous blood can be obtained before surgery. The risk for bleeding may be reduced by the preoperative injection of diluted vasopressin into the cervical stroma (178). The risk of injury to branches of the uterine artery can be lowered by limiting the depth of resection in the lateral endometrial cavity near the uterine isthmus, where ablative techniques should be considered. When bleeding is encountered during resectoscopic procedures, the ball electrode can be used to desiccate the vessel electrosurgically. Intractable bleeding may respond to the injection of diluted vasopressin or to the inflation of a 30-mL Foley catheter balloon or similar device in the endometrial cavity (132).

Thermal Trauma

Thermal injury to the intestine or ureter may be difficult to diagnose, and symptoms may not occur for several days to 2 weeks. Therefore, the patient should be advised of the symptoms that could indicate peritonitis.

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22

Hysterectomy

Thomas G. Stovall



- **Hysterectomy is one of the most commonly performed surgical procedures in the United States.**
- **Vaginal hysterectomy continues to be the procedure of choice unless this route is contraindicated.**
- **There appears to be no advantage to the routine use of supracervical hysterectomy when compared with total hysterectomy.**
- **Oophorectomy at the time of hysterectomy is associated with an increase in patient mortality, and it is currently recommended that ovarian conservation be considered until at least age 65 years.**
- **A number of concurrent surgical procedure may be performed safely at the time of hysterectomy.**

Hysterectomy is one of the most common surgical procedures performed. After cesarean delivery, it is the second most frequently performed major surgical procedure

in the United States (1). In 1965, there were 426,000 hysterectomies performed in the United States, with an average length of hospital stay of 12.2 days. This number reached its peak in 1985, when 724,000 procedures were reported, with the length of stay decreasing to 9.4 days. The number of hysterectomies performed in the United States declined to 544,000 in 1991, with an average length of stay of 4.5 days. Of these 544,000 hysterectomies, 408,000 (75%) were performed abdominally, and 136,000 (25%) were performed vaginally (2,3). However, by 1998, the number of hysterectomies performed had increased to more than 600,000 (4). Using 1987 age-specific hysterectomy rates and the population projections supplied by the U.S. Census Bureau, it is projected that there will be 824,000 hysterectomies in the year 2005 (5).

The rate of hysterectomy has varied between 6.1 and 8.6 per 1,000 women of all ages. A woman's chance of having a hysterectomy is dependent on a variety of factors, including her age, race, and where she lives, and the sex of her physician. Women between the ages of 20 and 49 years constituted the largest segment of women undergoing the procedure. **The average age of a woman undergoing hysterectomy is 42.7 years and the median age is 40.9 years, which has remained constant since the**

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1980s. About 75% of all hysterectomies are performed in women between the ages of 20 and 49 years. The rates of hysterectomy vary by region of the country. The highest overall rate is in the southern states, where the rate tends to be higher for women aged 15 to 44 years. The lowest rates have consistently been in the northeastern portion of the United States. Hysterectomy is more often performed in African American than in white women and is performed more frequently by male gynecologists than by female gynecologists (6,7,8,9).

Indications

The indications for hysterectomy are listed in Table 22.1. **In virtually all studies, uterine leiomyomas are consistently the leading indication for hysterectomy. As expected, the indications differ with the patient's age** (10). For instance, whereas pelvic support defects account for 16% of all hysterectomies, this diagnosis is responsible for more than 33% of hysterectomies in women older than 55 years of age. More complete discussions of these indications are presented in the specific chapters indicated.

Leiomyomas

Uterine leiomyomas are the most common pelvic tumors in women; therefore, this condition is responsible for a large number of hysterectomies (10). Hysterectomy for uterine leiomyomas should be considered only in patients who do not desire future fertility. Otherwise, fertility-preserving surgical management (myomectomy) is possible in most patients with leiomyomas. **The decision to perform a hysterectomy for leiomyomas is usually based on the need to treat symptoms**—abnormal uterine bleeding, pelvic pain, or pelvic pressure. Other indications for intervention have included “rapid” uterine enlargement (although this finding is poorly defined), ureteral compression, or uterine growth after menopause. **The concept of rapid growth has been challenged** (11) **because such patients have not been shown clearly to have malignant conditions.** Furthermore, there is no clearly reproducible definition of rapid growth. The removal of the uterus because it reaches a certain size is widely debated. In the past, surgeons removed the uterus if its size reached that approximating 12 weeks of gestation or greater, even if it was asymptomatic. The reasons given for such an intervention include the inability to palpate the ovaries on bimanual examination and the assumption that, as the uterus enlarges, the morbidity for hysterectomy increases. Malignancy is uncommon in premenopausal patients, however, and adnexal palpation is not possible in many patients whose ovaries are of normal size. If

the procedures are performed abdominally, there is no difference in surgical morbidity between patients with a 12-week-sized uterus and those with a 20-week-sized uterus (12). **Therefore, hysterectomy for leiomyomas should be considered only in symptomatic patients who do not desire future fertility (12).**

To reduce uterine size before hysterectomy, patients with large leiomyomas may be pretreated with a gonadotropin-releasing hormone (GnRH) agonist (13,14,15). In many cases, the reduction of uterine size is sufficient to permit vaginal hysterectomy when otherwise an abdominal hysterectomy would have been necessary. In one prospective trial, premenopausal patients with leiomyomas the size of 14 to 18 weeks of gestation were randomized to receive either 2 months of preoperative depot GnRH agonist or no GnRH agonist (15). Treatment with a short course (8 weeks) of *leuprolide acetate* before surgery enabled the procedures to be converted safely from an abdominal hysterectomy to a vaginal hysterectomy. This preoperative regimen was associated with a rise in hematocrit before surgery and, because patients were more likely to have vaginal than abdominal hysterectomy, a shorter hospital stay and convalescent period.

Table 22.1 Hysterectomy Indication Profile^a

Indication	No. of Patients	Percentage	Percentage Confirmed ^b
<i>Acute condition (emergencies)</i>			
A-1 Pregnancy catastrophe ¹	27	1.5	93
A-2 Severe infection ²	2	<1	100
A-3 Operative complication ¹	1	<1	100
<i>Benign disease</i>			
B-1 Leiomyomas ²	522	29	86
B-2 Endometriosis ²	95	5.3	92
B-3 Adenomyosis ²	27	1.5	44
B-4 Chronic infection ²	29	1.6	100
B-5 Adnexal mass ²	146	8.1	100
B-6 Other ²	1	<1	100
<i>Cancer or premalignant disease (known)</i>			
C-1 Invasive cancer ²	164	9.1	100
C-2 Preinvasive disease ²	137	7.6	100
C-3 Adjacent or distant cancer ²	6	<1	100
<i>Discomfort (chronic or recurrent)</i>			
D-1 Chronic pelvic pain ¹	144	8	80
D-2 Pelvic relaxation ¹	189	10.5	100
D-3 Stress urinary incontinence ¹	86	4.8	100
D-4 Abnormal uterine bleeding ¹	225	12.5	94
<i>Extenuating circumstances (peer reviewed)</i>			
E-1 Sterilization ³	3	<1	100
E-2 Cancer prophylaxis ³	5	<1	100
E-3 Other ³	2	<1	100
Total	1,811	100	92

^aInformation based on single designated (first-listed) preoperative diagnosis for 1,811 operations performed at Naval Hospitals in San Diego and Camp Pendleton, California, and UCLA Medical Center.

^bValidated by the American College of Obstetricians and Gynecologists criteria sets 1 or verified by tissue pathology 2 or preoperative peer review.³

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Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding is the indication for about 20% of hysterectomies.

Because dysfunctional uterine bleeding usually is the result of anovulation, the bleeding can be controlled by medical interventions with *progestin*, *estrogen*, a combination of *progestin* and *estrogen*, oral contraceptives, or nonsteroidal anti-inflammatory agents (see Chapter 14). In most patients, the bleeding requires no therapy unless anemia is present or bleeding is excessive and interferes with the patient's quality of life. In patients older than 35 years of age, endometrial sampling should be performed before hysterectomy. **Dilation and curettage is not an effective means of controlling bleeding and is not necessary before hysterectomy** (16). Therefore, **hysterectomy should be reserved for patients**

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who do not respond to or who cannot tolerate medical therapy. Alternatives to hysterectomy (eg, endometrial ablation or resection) should be considered in selected patients because these operations may be cost-effective and have a lower morbidity rate (see Chapter 21).

Intractable Dysmenorrhea

About 10% of adult women are incapacitated for up to 3 days per month as a result of dysmenorrhea (see Chapter 15) (17). Dysmenorrhea can be treated with nonsteroidal anti-inflammatory agents used alone or in combination with oral contraceptives or other hormone agents to reduce or ablate menstrual flow (18,19). Hysterectomy is rarely required for the treatment of primary dysmenorrhea. In patients with secondary dysmenorrhea, the underlying condition (e.g., leiomyomas, endometriosis) should be treated primarily.

Hysterectomy should be considered only if medical therapy fails or if the patient does not want to preserve fertility (20,21,22).

Pelvic Pain

In a review of 418 women in whom hysterectomy was performed for a variety of nonmalignant conditions, 18% had chronic pelvic pain. Preoperative laparoscopy was performed in only 66% of these patients. After hysterectomy, there was a significant reduction in symptoms associated with an improvement in the patient's quality of life (23). In a review of 104 patients who underwent hysterectomy for chronic pelvic pain that was believed to be of uterine origin, 78% experienced improvement in their pain after follow-up for a mean of 21.6 months (24). However, 22% of patients had no improvement in or exacerbation of their pain. **Hysterectomy should be performed only in those patients whose pain is of uterine origin and does not respond to nonsurgical treatments** (18) (see Chapter 15).

Cervical Intraepithelial Neoplasia

In the past, hysterectomy was performed as primary treatment of cervical intraepithelial neoplasia. However, the maximum depth of dysplasia at the squamocolumnar junction is 5.2 mm; 99.7% of dysplasias (including carcinoma *in situ*) are located within 3.8 mm of the epithelial surface (25). Therefore, **more conservative treatments such as cryotherapy, laser, or a loop electrosurgical excision procedure can be effective in treating the disease, making hysterectomy unnecessary in most women with these conditions** (see Chapter 17). For patients with recurrent high-grade dysplasia who do not desire to preserve fertility, hysterectomy is an appropriate treatment option. Even after hysterectomy, however, patients are at increased risk for vaginal intraepithelial neoplasia.

Genital Prolapse

Hysterectomy for symptomatic genital prolapse accounts for about 15% of hysterectomies performed in the United States (7). **Unless there is an associated condition requiring an abdominal incision, vaginal hysterectomy is the preferred approach for genital prolapse.** Uterine prolapse typically is not an isolated event and most often is associated with a variety of pelvic support defects (see Chapter 24). Each defect must be corrected to optimize the surgical outcome and decrease the risk of future development of pelvic support defects.

Obstetric Emergency

Most emergency hysterectomies are performed because of postpartum hemorrhage resulting from uterine atony. Other indications include uterine rupture that cannot be repaired or a pelvic abscess that does not respond to medical therapy. Hysterectomy may be required for patients with placenta accreta or placenta increta.

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Pelvic Inflammatory Disease

Pelvic inflammatory disease can generally be treated successfully with antibiotics. The uterus, tubes, and ovaries should not be removed in a patient with pelvic inflammatory disease unless the patient has not responded to intravenous antibiotic therapy (see Chapter 16). Whether one proceeds with conservative surgical management, abscess drainage, or organ removal is a subjective decision that must be based on the individual. If accessible, some pelvic abscesses may be drained successfully by percutaneous catheter drainage guided by ultrasonography or computed tomography (CT) scanning. Surgical intervention also is necessary if the patient has acute abdominal findings associated with peritonitis and signs of sepsis in the presence of a ruptured tubo-ovarian abscess. **For the patient who desires future fertility, consideration should be given to unilateral adnexectomy or partial bilateral adnexectomy without hysterectomy.** For the patient in whom bilateral adnexectomy is required, the uterus can be left in place for possible ovum donation and *in vitro* fertilization (see Chapter 30).

Endometriosis

Medical and conservative surgical procedures generally are successful for treatment of endometriosis (see Chapter 29). Therefore, **adnexectomy, with or without hysterectomy, should be performed only in patients who do not respond to conservative surgical** (resection or ablation of endometriotic implants) or medical therapy. Most patients with endometriosis who require hysterectomy have unrelenting pelvic pain

or dysmenorrhea. Other less common situations include patients who do not desire future fertility and who have endometriosis involving other pelvic organs, such as the ureter or colon.

Cancer

Metastases from nongynecologic sites may cause symptoms requiring hysterectomy. As a primary procedure, hysterectomy with bilateral salpingo-oophorectomy should be considered for patients with colorectal carcinoma because these patients are at risk for either synchronous pelvic cancers or occult metastases (26,27).

Benign Ovarian Tumor

Benign ovarian tumors that are persistent or symptomatic require surgical treatment. Obviously, if the patient desires fertility, the uterus should be conserved. If fertility is not an issue, however, or if the patient is perimenopausal or postmenopausal, a decision must be made regarding whether the uterus should be removed. In a one study, 100 patients who underwent adnexectomy plus hysterectomy for benign adnexal disease were compared with a group of risk-matched women who underwent adnexectomy without hysterectomy for the same indication (28). There was a significant increase in operative morbidity, estimated blood loss, and the length of hospital stay for patients in whom hysterectomy was performed.

Vaginal versus Abdominal Hysterectomy

The proportion of abdominal versus vaginal hysterectomies has not changed significantly since the 1980s—about 75% of hysterectomies are abdominal (2,3,7,29,30,31,32). There are no specific criteria that can be used to determine the route of hysterectomy. The route chosen should be based on the individual patient. Absolute and relative contraindications have been proposed (27,28,29). In a large, multicenter retrospective study conducted by the U.S. Centers for Disease Control and Prevention between 1978 and 1981, the risks and outcome of abdominal and vaginal hysterectomy were compared (32). The study included 1,851 patients aged 15 to 44 years in whom hysterectomy was performed for

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benign gynecologic disorders (568 vaginal, 1,283 abdominal). Surgical complications were classified into six categories. The overall complication rate was 24.5 per 100 for vaginal hysterectomy compared with 42.8 per 100 women for abdominal hysterectomy. **The risk for one or more complications after abdominal hysterectomy was 1.7 times the risk after vaginal hysterectomy.** The two major categories of complications were febrile morbidity and hemorrhage requiring transfusion. **The risk for febrile morbidity was 2.1 times higher for abdominal hysterectomy than for vaginal hysterectomy, and the risk for transfusion was 1.9 times higher for abdominal surgery.** Since the collection of these data, transfusion practices within the United States have changed as a result of increased awareness of the human immunodeficiency virus. Although only one fourth of hysterectomies are performed vaginally, this proportion could probably be increased substantially. In a study of 617 hysterectomies, 548 were performed vaginally; laparoscopic assistance was used in 63 patients, and an abdominal approach was required in only 6 patients (33). If feasible, vaginal hysterectomy is the preferred approach.

Supracervical Hysterectomy

The indications for supracervical hysterectomy are somewhat vague. Potential indications include endometriosis with obliteration of the anterior and posterior cul-de-sac, cesarean hysterectomy when the cervix is fully dilated and difficult to identify, and concern

for sexual function. During a technically difficult surgical procedure (e.g., obliteration of the cul-de-sac), there may be concern about the potential morbidity associated with the removal of the cervix. However, **the cervix can almost always be removed**. Some women desire to conserve the cervix because they believe that it is important for sexual satisfaction, although there are no sound scientific data to prove this perception. Some authors (currently representing the minority view) believe that the cervix should not be removed unless there is a specific reason. They suggest that removal of the cervix leads to a decrease in sexual pleasure, increased operative and postoperative morbidity, vaginal shortening, vault prolapse, abnormal cuff granulations, and the potential for oviductal prolapse (34,35).

There is a debate about the effects of leaving the cervix *in situ*. In a study of a group of 210 patients who underwent hysterectomy, one half had total abdominal hysterectomies and one half had supracervical hysterectomies (36). Studies of the same population disclosed an increase in psychiatric symptoms in both groups (34,35,36). Sexual desire and functioning was unchanged, although both groups experienced a decrease in dyspareunia. Patients undergoing supracervical hysterectomy were reported to have increased orgasmic frequency when compared with patients in whom the cervix was left intact (36,37,38,39). **In a clinical trial, 135 women were randomized to undergo total abdominal hysterectomy or supracervical hysterectomy. After 2-year follow-up, both groups had similar sexual functioning and health-related quality of life** (40). Regardless of the reason for leaving the cervix at the time of hysterectomy, preoperative Papanicolaou (Pap) test results must be normal, and appropriate consent must be obtained from the patient.

Laparoscopically Assisted Hysterectomy

Laparoscopy has been used diagnostically before hysterectomy (see Chapter 21). In a study of laparoscopy performed in 46 patients who had been advised to have abdominal hysterectomies, the findings suggested that the referring physicians had overestimated uterine size and underestimated uterine mobility (33). All 14 patients who were referred for assessment of adnexal pathology had none. In 91% (42 of 46) of the patients, vaginal hysterectomy was performed. Another study evaluated seven patients who, aside from their histories suggestive of adhesions, were candidates for vaginal hysterectomy (41). Six

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of the patients underwent laparoscopy, which did not reveal any adhesive disease, and were able to undergo vaginal hysterectomy. These findings are consistent with the other data demonstrating that the **presence of pelvic adhesions cannot be predicted based on either history or physical examination** (42). If laparoscopy is performed on patients with risk factors for adhesions or endometriosis, however, many patients will undergo the procedure needlessly, and about one half of those with adhesions or endometriosis will be overlooked. Thus, the role of diagnostic laparoscopy immediately before hysterectomy seems limited.

The use of operative laparoscopy to complete some or all of the hysterectomy has been widely reported (43,44,45,46,47,48,49,50,51,52,53) (see Chapter 21). However, in most of these studies, the patient population was neither randomized nor defined. Furthermore, the reasons the patient would require an abdominal approach are unclear. **The criteria for selection of patients for laparoscopically assisted vaginal hysterectomy (LAVH) versus abdominal hysterectomy have not been clearly established.**

In a prospective, controlled trial, patients who were candidates for vaginal hysterectomy were randomized to either LAVH or a standard vaginal approach (47). All procedures were performed on an outpatient basis; included were patients who had uterine leiomyomas up to the size of 16 weeks of gestation. There was no difference between the groups in terms of

uterine weight, febrile morbidity, or the need for transfusion. Patients undergoing LAVH had a lower hematocrit value on the first and second postoperative days and required more pain medication on the second postoperative day. Although these findings are not clinically significant, they suggest that, when compared with a vaginal approach, LAVH does not reduce perioperative morbidity. The cost of LAVH is significantly higher than that of vaginal hysterectomy; the largest component of this cost differential resulted from the use of disposable equipment. **This study demonstrates that there is no advantage of LAVH over traditional vaginal hysterectomy.**

It has been suggested that LAVH may be helpful in treating patients with documented endometriosis, known pelvic adhesive disease, an adnexal mass that requires hysterectomy, and lack of uterine mobility (see Chapter 21). Depending on the circumstances, LAVH may be appropriate in some patients with stage I endometrial cancer or previous episodes of multiple major pelvic surgery. For example, if the patient has had endometriosis that has been treated previously or adhesions that have been lysed previously and now require hysterectomy, a vaginal approach can most likely be taken. In a study of a group of patients with stage III or IV endometriosis, the procedure was successful in 40 of 46 patients (54). Even in the hands of expert laparoscopic surgeons, however, the rate of complications was high.

Mild pelvic adhesions do not preclude vaginal hysterectomy. If the patient has intensive adhesions that involve the adnexa, bowel, and uterus, however, an abdominal approach usually is needed (55). In such patients, laparoscopy may be a better alternative than hysterectomy.

It is uncertain whether LAVH is preferable in patients with limited uterine mobility, and there is no standard method to assess the best approach. The major supporting structures of the uterus are the uterosacral ligaments and lower cardinal complex (56), which are not generally transected with a laparoscopic approach. Transection of the utero-ovarian ligament, round ligament, and broad ligament does not improve mobility.

Both LAVH and pelvic lymphadenectomy may be useful in selected patients with endometrial carcinoma (57). The data suggest that a lymphadenectomy can be performed successfully and that hospital stay and morbidity are decreased when compared with the standard transabdominal approach. Long-term prospective studies are needed to address these questions.

Concurrent Surgical Procedures

Oophorectomy

A laparoscopic approach should not be used in conjunction with hysterectomy solely for the purpose of accomplishing ovarian removal. Although not every ovary can be removed through the vagina, it has been shown clearly that most can be removed in this manner (58).

Prophylactic oophorectomy is the most common surgical procedure performed concurrently with hysterectomy. Oophorectomy is performed prophylactically to prevent ovarian cancer and to eliminate the potential need for further surgery for either benign or malignant disease. However, the optimal age for this prophylactic oophorectomy in women who have increased risk as well as those who do not have increased risk has not been determined. **Arguments against prophylactic oophorectomy center on the need for earlier and more prolonged hormone therapy and the potential increase risk of cardiovascular disease** (59,60). Although hormone therapy generally is well tolerated and provides

good symptomatic relief, it may not be as effective as normal ovarian function, and the implications of long-term hormone therapy are not fully known. Therefore, the decision to proceed with oophorectomy should be considered carefully after the patient has been informed of the risks and benefits.

The risk for developing ovarian cancer after hysterectomy for benign disease is lower than would be expected based on its prevalence. Of those women who have no history of ovarian tumors and normal-appearing ovaries at the time of abdominal hysterectomy, 0.14 to 0.47% subsequently develop ovarian cancer in their conserved ovaries (59,60). Considering that as many as 1.4% of women are expected to get ovarian cancer, this is about one tenth to one third the expected rate. Presumably, this lower rate occurs because the cohort of women with normal-appearing ovaries in whom hysterectomy is performed for benign disease is a "selected" population, and because it excludes patients at high-risk for developing ovarian cancer. In women who do not have ovarian disease at the time of hysterectomy, the risk for developing benign ovarian tumors is less than 5% (61). The risk for ovarian cancer in women with a strong family history is 3% to 50%, depending on the pedigree (62,63) (see Chapter 35).

Long-term compliance with posthysterectomy estrogen therapy is low (64). Only 20% to 40% of women who initiate treatment after hysterectomy and bilateral oophorectomy continue to take estrogen for more than 5 years. Therefore, it should not be assumed that patients will receive adequate estrogen after oophorectomy. Women who subsequently develop breast cancer may be advised not to take estrogen.

A Markov decision analysis model has been used to estimate the best strategy for maximizing a woman's survival when oophorectomy is considered in low-risk women undergoing hysterectomy for benign disease. Researchers found that women who had oophorectomy before age 55 years had an 8.58% excess mortality by age 80, and those with oophorectomy before age 59 have a 3.92% excess mortality. By age 75 years, this excess mortality is less than 1%.

The conclusion was that ovarian conservation until at least age 65 years confers long-term survival benefits for those women at average risk for ovarian cancer undergoing hysterectomy for benign disease (60).

Appendectomy

Appendectomy may be performed concurrently with hysterectomy to prevent appendicitis and to remove disease that may be present. The former use is of limited value, however, because the peak incidence of appendicitis is between 20 and 40 years of age, whereas the peak age for hysterectomy is 10 to 20 years later (65). Appendectomy is effective in removing previously undetected disease, but the likelihood that these

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abnormalities would cause any clinical problems is uncertain. In one study, histologic abnormalities were found in 71% (32 of 45) of appendices removed at the time of hysterectomy, and two had asymptomatic carcinoid tumors (66). In another study, 22% of appendices removed at the time of hysterectomy showed evidence of pathologic alterations, and five carcinoid tumors were identified (67).

There is no increase in morbidity associated with appendectomy performed at the time of hysterectomy (67,68,69), **although it does require an average of 10 minutes additional operating time** (60). Thus it is felt that incidental appendectomies in all abdominal hysterectomies could reduce the morbidity of appendicitis at a later time (70). Appendectomy has also been performed with vaginal hysterectomy without

additional intraoperative or postoperative morbidity (71,72,73,74).

Cholecystectomy

Gallbladder disease is about four times more common in women than men, and its highest incidence occurs between 50 and 70 years of age, when hysterectomy is most often performed. Thus, women may require both procedures. A combined procedure does not appear to result in increased febrile morbidity or length of hospital stay (75,76).

Abdominoplasty

Abdominoplasty performed at the time of hysterectomy is associated with a shorter hospital stay, a shorter operating time, and a lower intraoperative blood loss than when the two operations are performed separately (77,78). Liposuction also can be performed safely at the time of vaginal hysterectomy (79).

Technique

Negative results of a Pap test done within the year should be obtained before performing a hysterectomy for benign disease. If the patient is 40 years of age or older and has not recently had a mammography, this examination should be performed. Endometrial sampling is recommended if the patient has reported abnormal uterine bleeding. In patients older than 40 years of age, a stool guaiac test should be performed. Other preoperative testing should be dictated by the patient's specific medical conditions.

Abdominal Hysterectomy

Preoperative Preparation

Although not mandatory, a cleansing tap water or soap enema given on the evening before or the morning of the scheduled hysterectomy is preferred by some surgeons. To reduce the colony count of skin bacteria, the patient is asked to shower. Hair surrounding the incision area may be removed at the time of surgery or before surgery using a depilatory agent. Hair clipping is preferable to shaving because it decreases the incidence of incisional infection (80).

Patient Positioning

The patient is placed in the dorsal supine position for the procedure. After the patient is anesthetized adequately, her legs are placed in the stirrups and a pelvic examination is performed to validate the in-office pelvic examination findings. A Foley catheter is placed in the bladder, and the vagina is cleansed with an iodine solution. The patient's legs are then straightened.

Skin Preparation

Several methods for skin cleaning can be recommended, including a 5-minute iodine solution

scrub followed by application of iodine solution, iodine solution scrub followed by alcohol with application of an iodine-impregnated occlusive drape, or an iodine-alcohol combination with or without application of an iodine-impregnated occlusive drape.

Surgical Technique

Incision

The choice of incision should be determined by the following considerations:

- **Simplicity of the incision**
- **The need for exposure**
- **The potential need for enlarging the incision**
- **The strength of the healed wound**
- **Cosmesis of the healed incision**
- **The location of previous surgical scars**

The skin is opened with a scalpel, and the incision is carried down through the subcutaneous tissue and fascia. With traction applied to the lateral edges of the incision, the fascia is divided. The peritoneum is opened similarly. This technique minimizes the possibility of inadvertent enterotomy, entering the abdominal cavity.

Abdominal Exploration

After entering the peritoneal cavity, the upper abdomen and the pelvis are explored systematically. The liver, gallbladder, stomach, kidneys, para-aortic lymph nodes, and large and small bowel should be examined and palpated. Cytologic sampling of the peritoneal cavity, if needed, should be performed before abdominal exploration.

Retractor Choice and Placement

A variety of retractors have been designed for pelvic surgery. The Balfour and the O'Connor-O'Sullivan retractors are used most often. The Bookwalter retractor has a variety of adjustable blades that can be helpful, particularly in obese patients.

Elevation of the Uterus

The uterus is elevated by placing broad ligament clamps at each cornu so that it crosses the round ligament. The clamp tip may be placed close to the internal os. This placement provides uterine traction and prevents backbleeding (Fig. 22.1).

Round Ligament Ligation or Transection

The uterus is deviated to the patient's left side, stretching the right round ligament. With the proximal portion held by the broad ligament clamp, the distal portion of the round ligament is ligated with a suture ligature or simply transected with Bovie cautery (Fig. 22.2). The

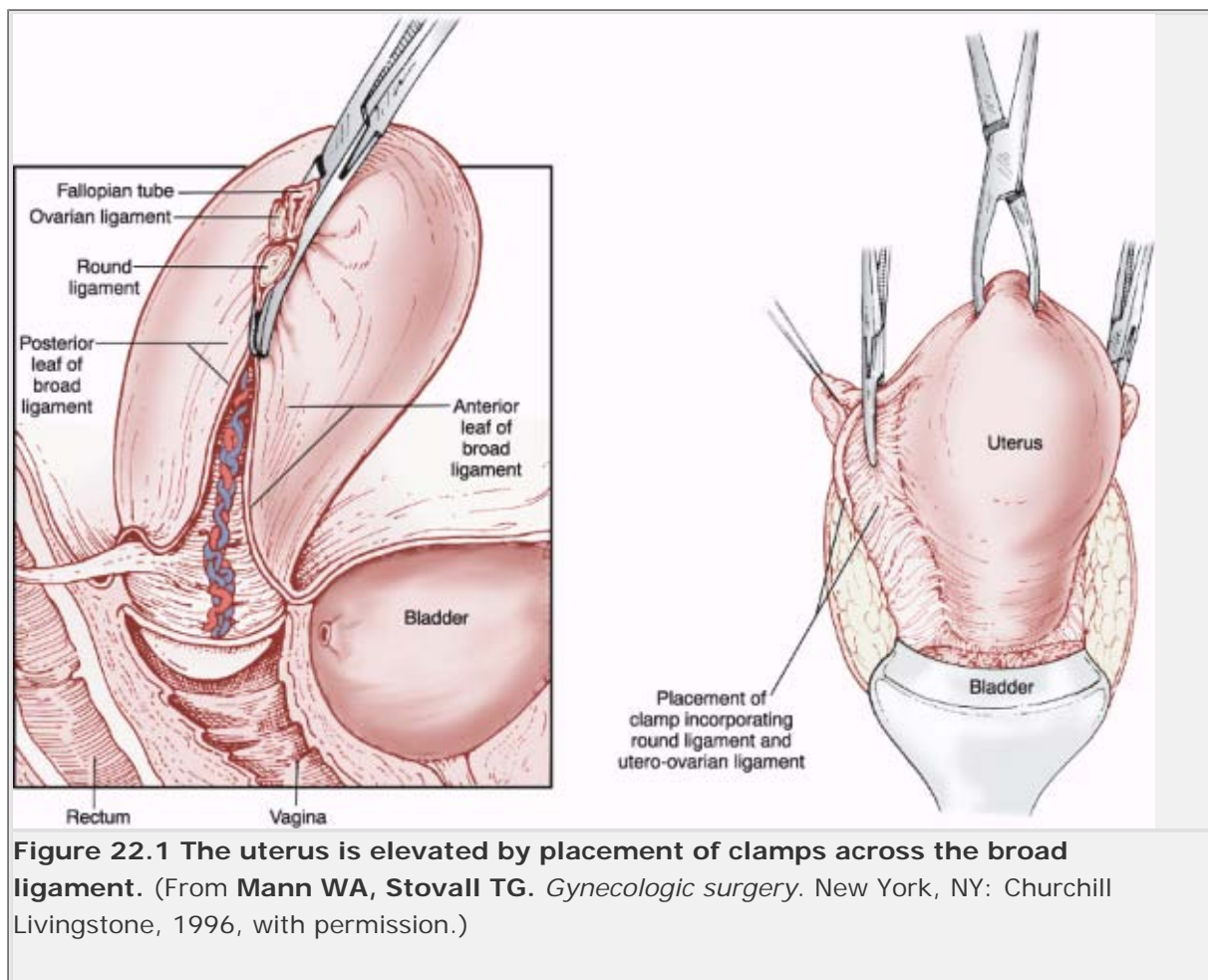
distal portion can be grasped with forceps, and the round ligament is cut to separate the anterior and posterior leaves of the broad ligament. The anterior leaf of the broad ligament is incised with Metzenbaum scissors or electrocautery along the vesicouterine fold, separating the peritoneal reflection of the bladder from the lower uterine segment (Fig. 22.3).

Ureter Identification

The retroperitoneum is entered by extending the incision cephalad on the posterior leaf of the broad ligament. Care must be taken to remain lateral to both the infundibulopelvic ligament and iliac vessels. The external iliac artery courses along the medial aspect of the psoas muscle and is identified by bluntly dissecting the loose alveolar tissue overlying it. **By following the artery cephalad to the bifurcation of the common iliac**

artery, the ureter is identified crossing the common iliac artery. The ureter should be left attached to the medial leaf of the broad ligament to protect its blood supply (Fig. 22.4).

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Utero-ovarian or Infundibulopelvic Ligament Ligation

If the ovaries are to be preserved, the uterus is retracted toward the pubic symphysis and deviated to one side, placing tension on the contralateral infundibulopelvic ligament, the tube, and the ovary. **With the ureter under direct visualization, a window is created in the peritoneum of the posterior leaf of the broad ligament under the utero-ovarian ligament and fallo-pian tube.** The tube and utero-ovarian ligament are clamped on each side with a curved Heaney or Ballentine clamp, cut, and ligated with both a free-tie and a suture ligature. The medial clamp at the uterine cornu should control backbleeding; if it does

not, the clamp should be repositioned to do so (Fig. 22.5).

If the ovaries are to be removed, the peritoneal opening is enlarged and extended cephalad to the infundibulopelvic ligament and caudad to the uterine artery. This opening allows proper exposure of the uterine artery, the infundibulopelvic ligament, **and the ureter.** In this manner, the ureter is released from its proximity to the uterine vessels and the infundibulopelvic ligament.

A curved Heaney or Ballentine clamp is placed lateral to the ovary (Fig. 22.6); care is taken to ensure that the entire ovary is included in the surgical specimen. The infundibulopelvic ligament on each side is cut and doubly ligated (Fig. 22.7). Alternatively, free ties

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can be passed around the infundibulopelvic ligament, two cephalad and one caudad, before the ligament is cut.

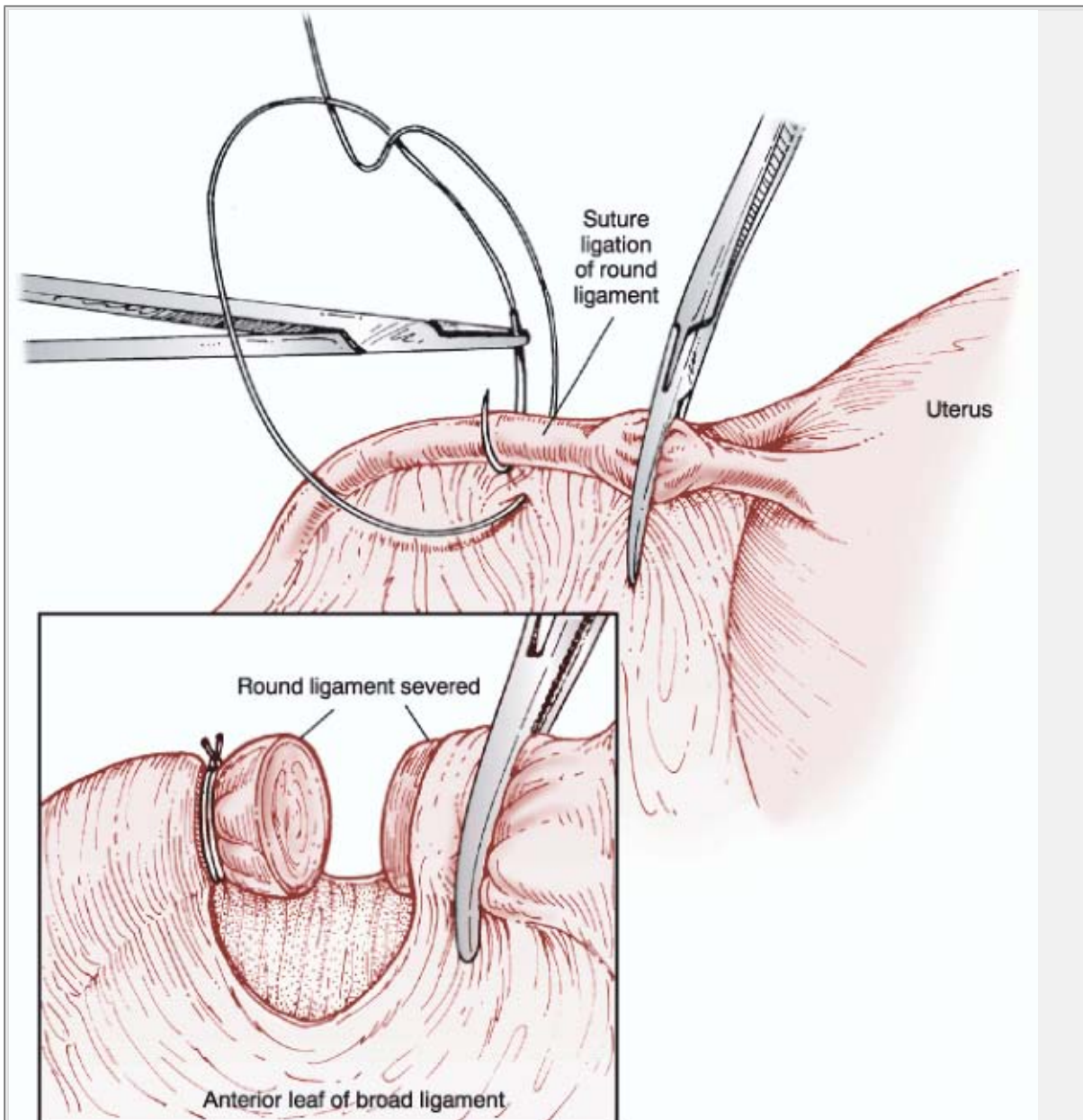


Figure 22.2 The round ligament is transected and the broad ligament is incised and opened. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Bladder Mobilization

Using Metzenbaum scissors, with the tips pointed toward the uterus, the bladder is sharply dissected from the lower uterine segment and cervix. Alternatively, Bovie electrocautery can be used. An avascular plane, which exists between the lower uterine segment and the bladder, allows for this mobilization. Tonsil clamps may be placed on the bladder edge to provide countertraction and easier dissection (Fig. 22.8).

Uterine Vessel Ligation

The uterus is retracted cephalad and deviated to one side of the pelvis, stretching the lower ligaments. The uterine vasculature is dissected or "skeletonized" from any remaining areolar tissue, and a curved Heaney clamp is placed perpendicular to the uterine artery at the junction of the cervix and body of the uterus. Care is taken to place the tip of the clamp adjacent to the uterus at this anatomic narrowing. The vessels are cut, and the suture is ligated. The same procedure is repeated on the opposite side (Fig. 22.9).

Incision of Posterior Peritoneum

If the rectum is to be mobilized from the posterior cervix, the posterior peritoneum between the uterosacral ligaments just beneath the cervix

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and rectum may be incised (Fig. 22.10). A relatively avascular tissue plane exists in this area, allowing mobilization of the rectum inferiorly out of the operative field. A sponge may be placed to control the venous oozing that often occurs.

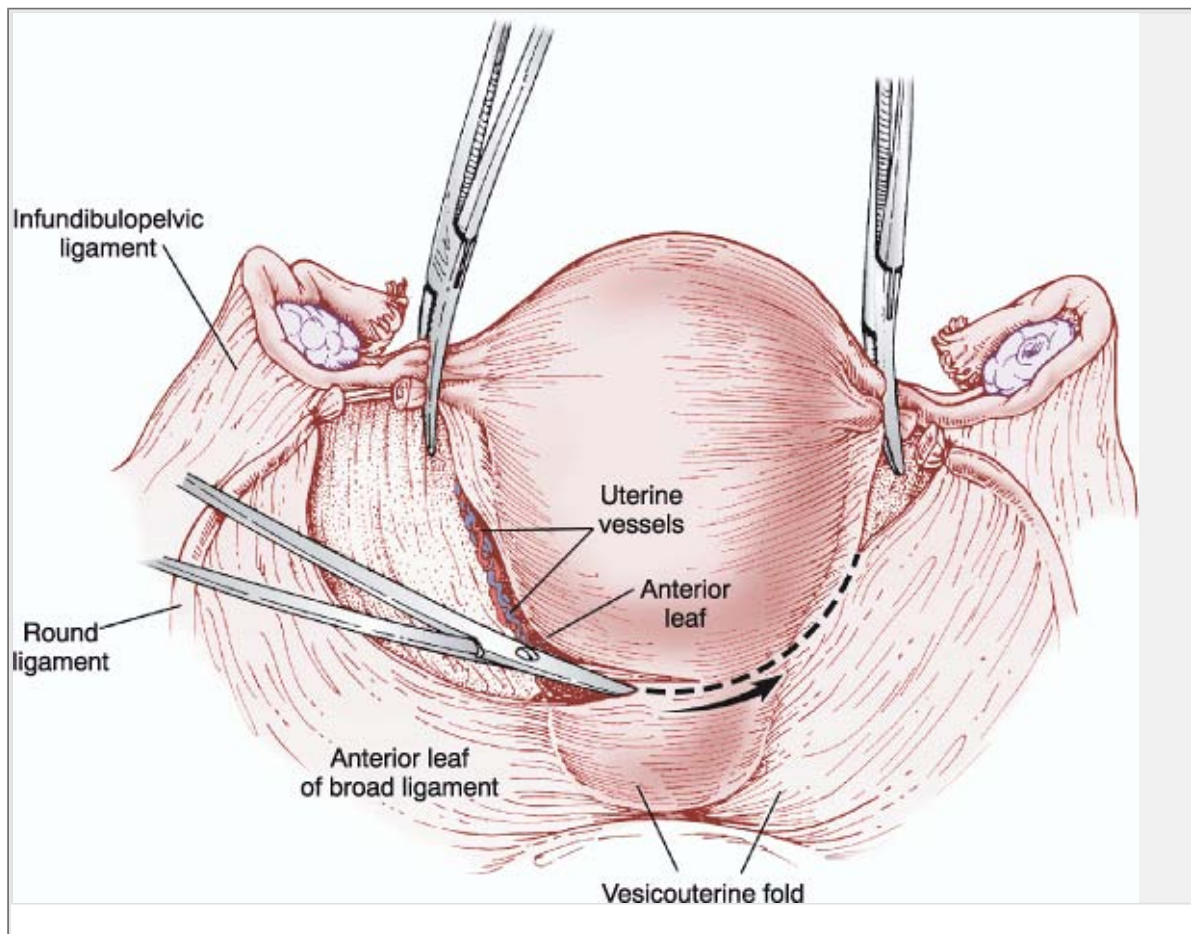


Figure 22.3 The incision in the anterior broad ligament is extended along the vesicouterine fold. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Cardinal Ligament Ligation

The cardinal ligament is divided by placing a straight Heaney clamp medial to the uterine vessel pedicle for a distance of 2 to 3 cm parallel to the uterus. The ligament is then cut, and the pedicle suture is ligated. This step is repeated on each side until the junction of the cervix and vagina is reached (Fig. 22.11).

Removal of the Uterus

The uterus is placed on traction cephalad, and the tip of the cervix is palpated. Curved Heaney clamps are placed bilaterally, incorporating the uterosacral ligament and upper vagina just below the cervix. **Care should be taken to avoid foreshortening the vagina.** The uterus is then removed with heavy, curved scissors (Fig. 22.12).

Vaginal Cuff Closure

Several techniques of vaginal cuff closure have been described. A figure-of-eight suture of 0-0 braided absorbable material is placed between the tips of the two clamps. The suture is used for both traction and hemostasis. Sutures are also placed at the tip of each clamp, and the pedicles are sutured with a Heaney stitch, thereby incorporating the uterosacral and cardinal ligament at the angle of the vagina (Fig. 22.13). Alternatively, the vaginal cuff can be left open to heal secondarily. If this method is used, a running-locked suture is used for hemostasis along the cuff edge (Fig. 22.14).

Irrigation and Hemostasis

The pelvis is thoroughly irrigated with saline or lactated Ringer's solution. Meticulous care is taken to ensure hemostasis throughout the pelvis, particularly of the vascular pedicles. Ureteral position and integrity are checked again to ensure that they are intact and do not appear dilated.

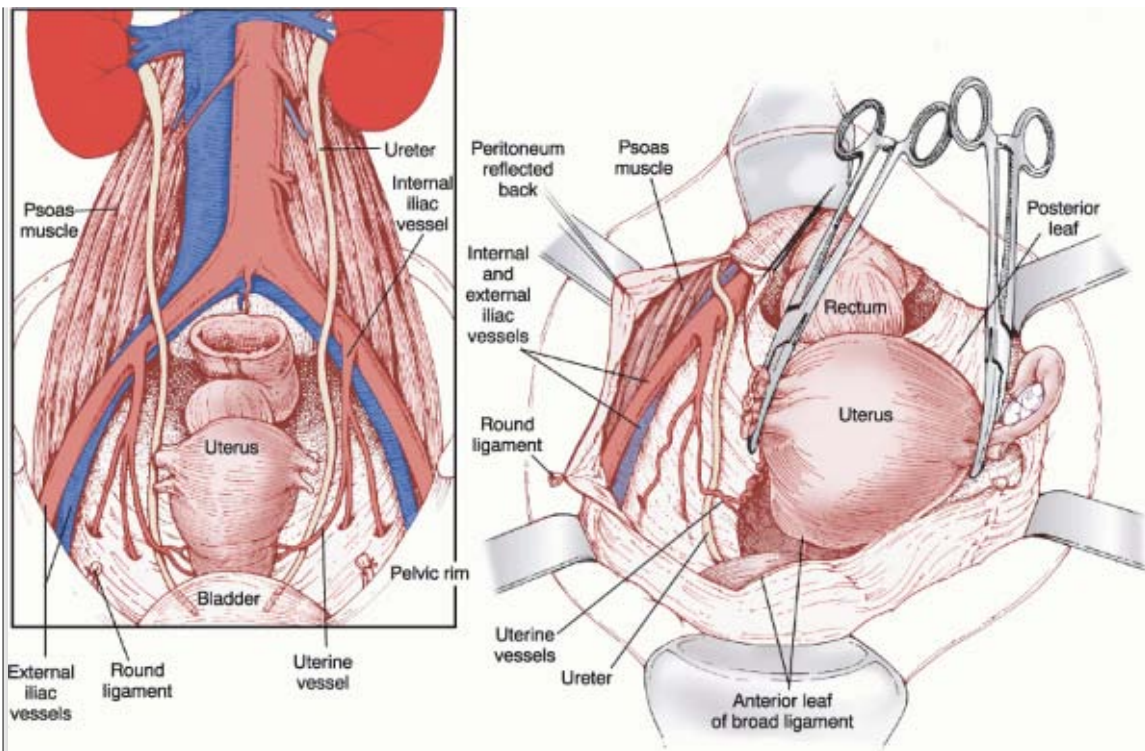


Figure 22.4 Identification of the ureter in the retroperitoneal space on the medial leaf of the broad ligament. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

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Peritoneal Closure

The pelvic peritoneum is not reapproximated. Research using animal models suggests that reapproximation may increase tissue trauma and promote adhesion formation (80). If the ovaries have been retained, they may be suspended to the pelvic sidewall to minimize the risk of becoming retroperitoneal or adherent to the vaginal cuff.

Incision Closure

The parietal peritoneum is not reapproximated as a separate layer. Fascia can be closed with an interrupted or a continuous 0-0 or 1-0 monofilament absorbable suture. A continuous suture may reduce the risk for necrosis, which may occur when interrupted sutures are tied too tightly (80). As with interrupted sutures, bites should be taken about 1 cm from the cut edge of the fascia and about 1 cm apart to prevent wound dehiscence.

Skin Closure

The subcutaneous tissue should be irrigated, with careful attention given to maintaining hemostasis. Subcutaneous sutures are not used because they may increase the incidence of wound infection (80). Skin staples or subcuticular sutures are used to reapproximate the skin edges. A bandage is applied and left in place for about 24 hours.

Intraoperative Complications

Most intraoperative injuries during abdominal hysterectomy can be traced to poor

lighting, unsatisfactory assistance, undue haste, anatomic variants, or involvement of the injured organ in the disease process (81). Some of these factors can be eliminated with careful attention to detail and use of proper surgical technique. However, some operative injuries

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cannot be avoided by even the most skilled surgeons. The surgeon, therefore, must be prepared to recognize and repair these injuries. Even with a high level of attention to detail, injuries and complications, recognized and unrecognized, can still occur.

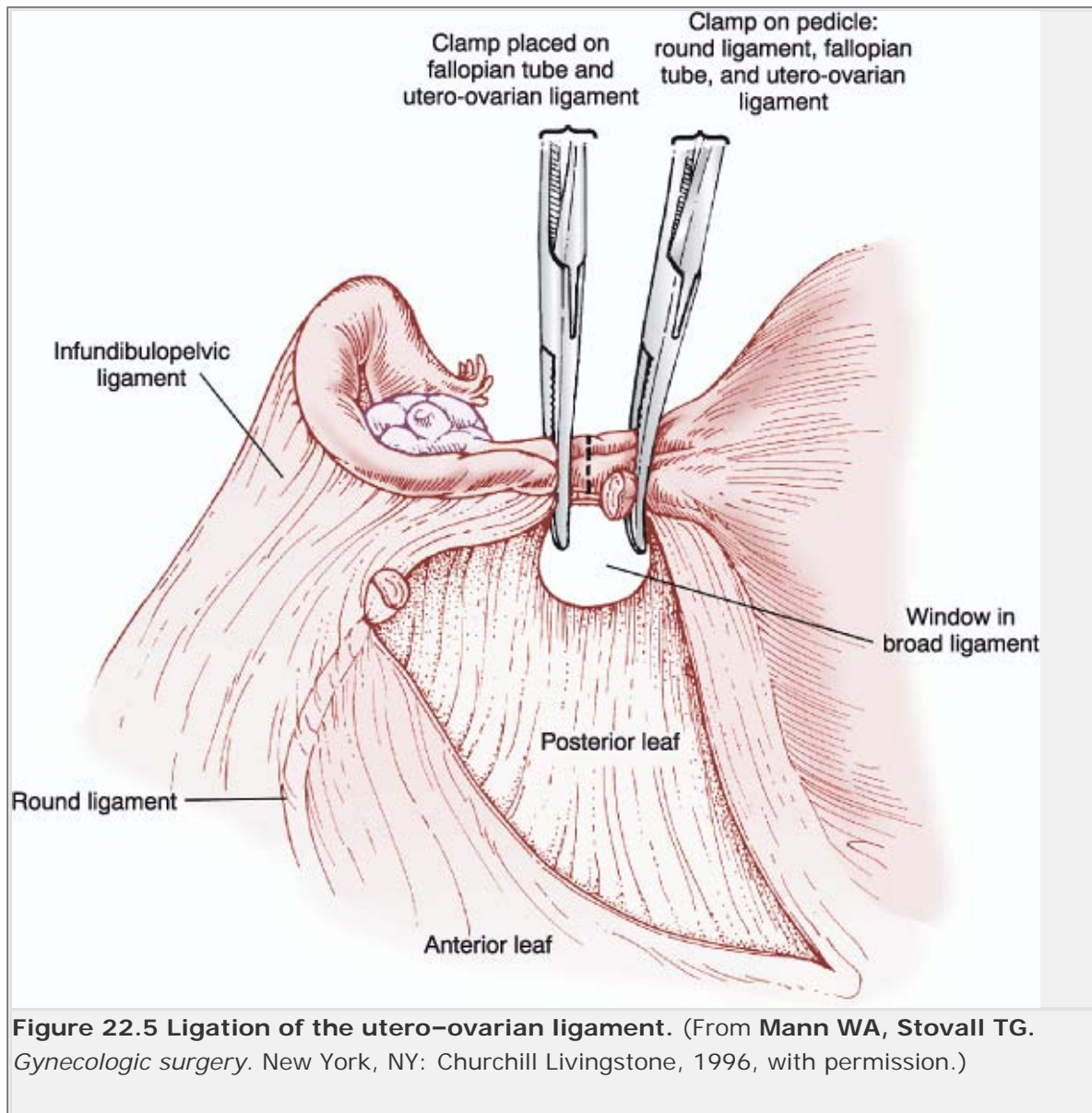


Figure 22.5 Ligation of the utero-ovarian ligament. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

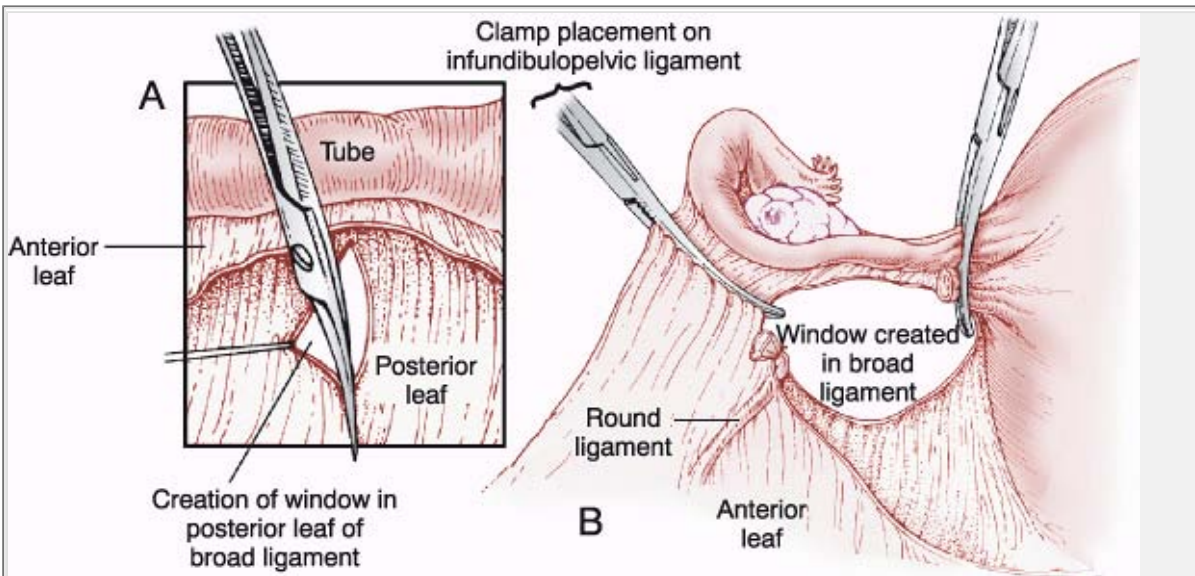


Figure 22.6 Ligation of the infundibulopelvic ligament. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

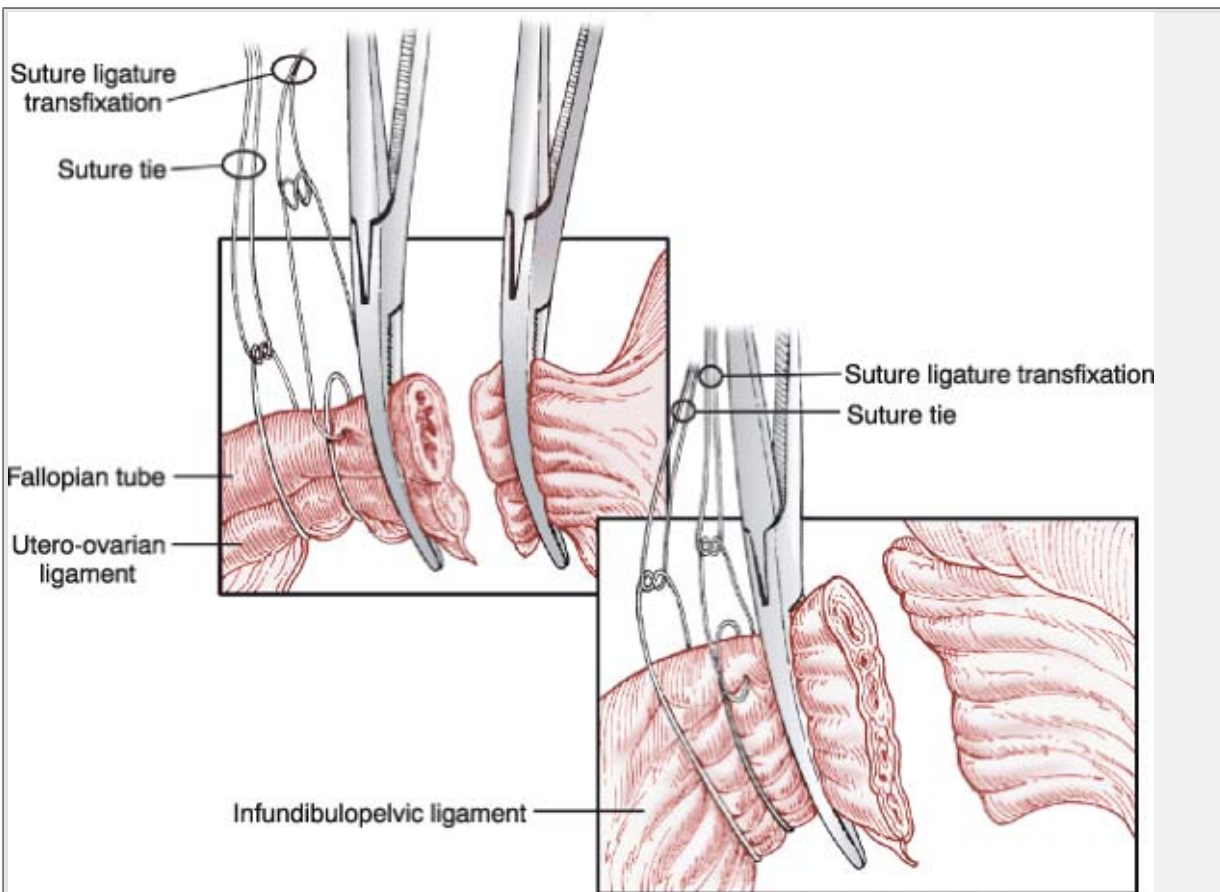


Figure 22.7 Transection of the infundibulopelvic ligament. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Ureteral Injuries

Injury to the pelvic ureter is one of the most formidable complications of hysterectomy (82,83,84). Because of the risk for subsequent renal impairment, injury to the ureter is far more serious than injury to the bladder or bowel (85,86).

It is essential to be aware of the proximity of the ureter to the other pelvic structures at all times. **Most ureteral injuries can be avoided by opening the retroperitoneum and directly identifying the ureter.** The use of ureteral catheters as a substitute for direct visualization is often of little help in patients with extensive fibrosis or scarring resulting from endometriosis, pelvic inflammatory disease, or ovarian cancer. In these instances, a false sense of security may actually increase an already high risk for ureteral injury (87). The use of ureteral catheters can also be associated with hematuria and acute urinary retention. Their complications are usually transitory in nature.

Direct visualization is accomplished by opening the retroperitoneum lateral to the external iliac artery. Blunt dissection of the loose areolar tissue is performed to visualize the artery directly. The artery may then be traced cephalad to the bifurcation of the internal and external iliac arteries. The ureter crosses the common iliac artery at its bifurcation and may be followed throughout its course in the pelvis.

Despite these precautions, ureteral injuries may occur. Prompt consultation is necessary if the surgeon has not been trained in ureteral repair. If a ureteral obstruction is suspected, confirmation may be obtained by intravenous injection of 1 ampule of *indigo carmine* dye,

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opening the dome of the bladder, and observing the presence or absence of bilateral spill of tinted urine. Alternatively, ureteral patency may be established by opening the dome of the bladder and positioning retrograde ureteral stents. Cystoscopic evaluation may replace opening the bladder to evaluate the spill of tinted urine (82,83,84,85,86,87).

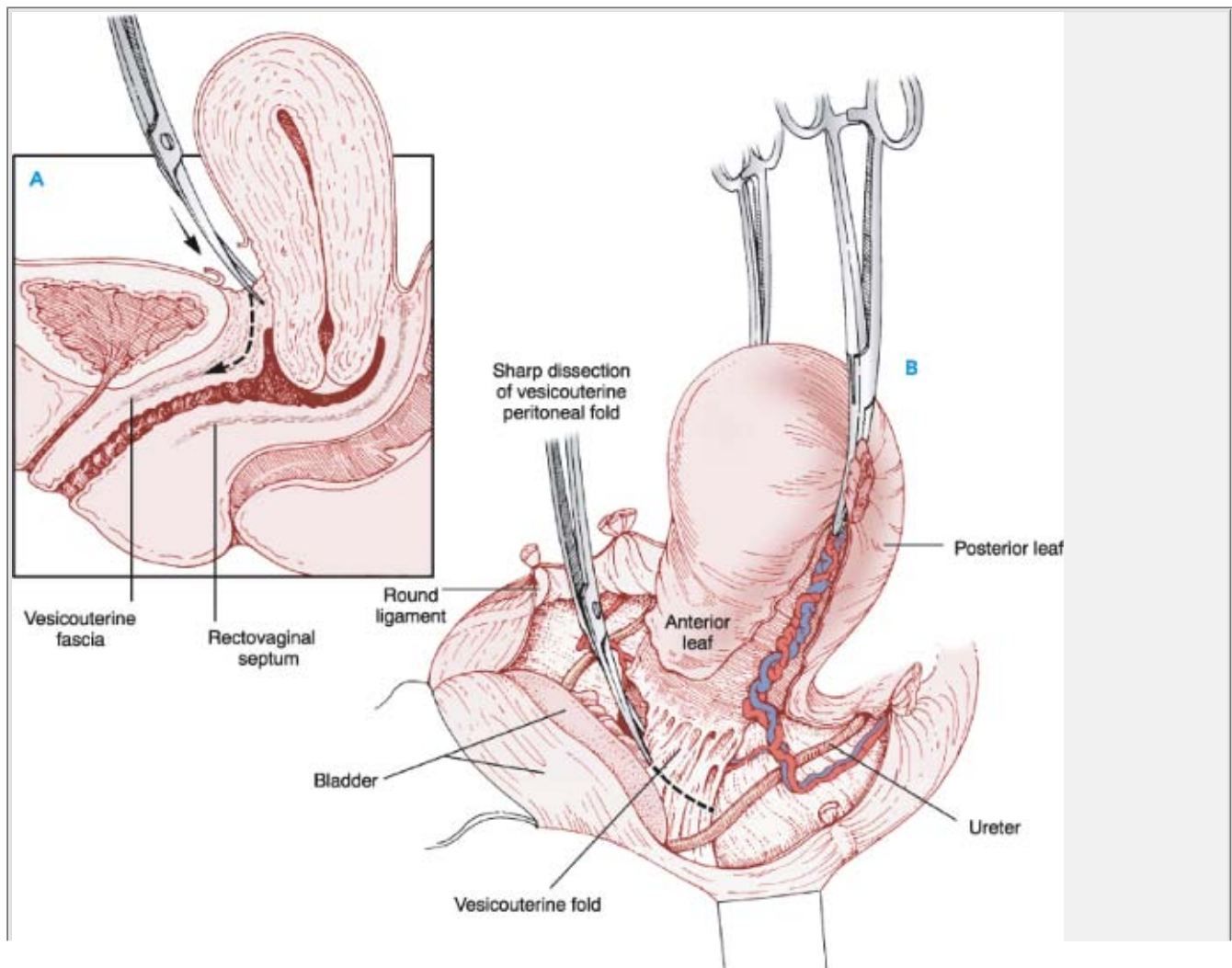


Figure 22.8 Dissection of the vesicouterine plane to mobilize the bladder. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Bladder Injury

Because of the close anatomic relationship of the bladder, uterus, and upper vagina, the bladder is the segment of the lower urinary tract that is most vulnerable to injury (85,87). **Bladder injury may occur on opening the peritoneum or, more frequently, during the dissection of the bladder off the cervix and upper vagina** (88). Unless there is involvement of the bladder trigone, a bladder laceration is easily repaired. In the nonirradiated bladder, a one- or two-layer closure with a small-caliber braided absorbable suture such as a 3-0 polyglycolic acid is adequate. The bladder should be drained postoperatively. The length of time that drainage is required is controversial. If the bladder is not compromised, drainage should be continued at least until gross

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hematuria clears, which may occur as soon as 48 hours postoperatively. A more conservative practice is to continue drainage until the patient is ready for discharge, usually a total of 3 to 4 days. Elective incision into the dome of the bladder is performed similarly (88). If the trigone is involved, a surgeon trained in complicated urologic repair should be consulted.

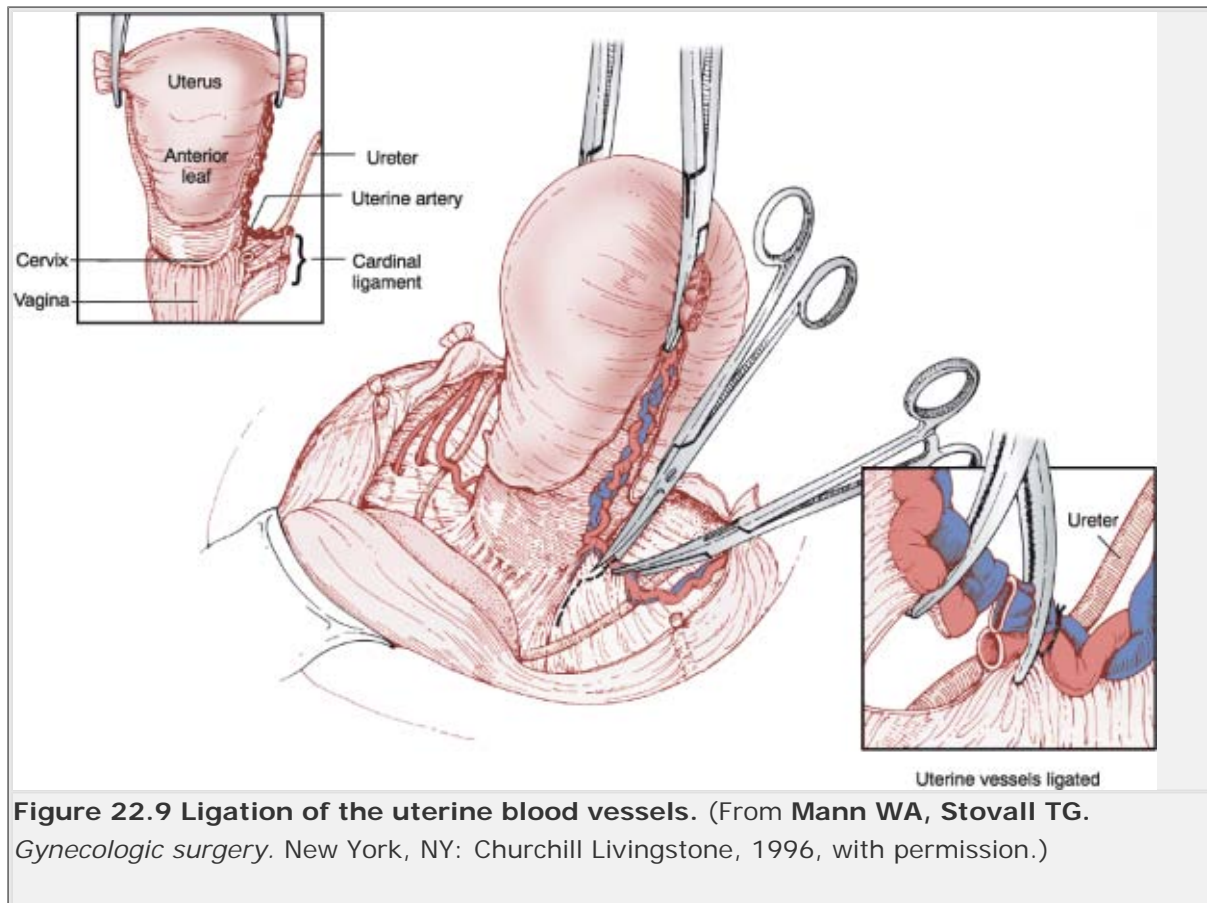


Figure 22.9 Ligation of the uterine blood vessels. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

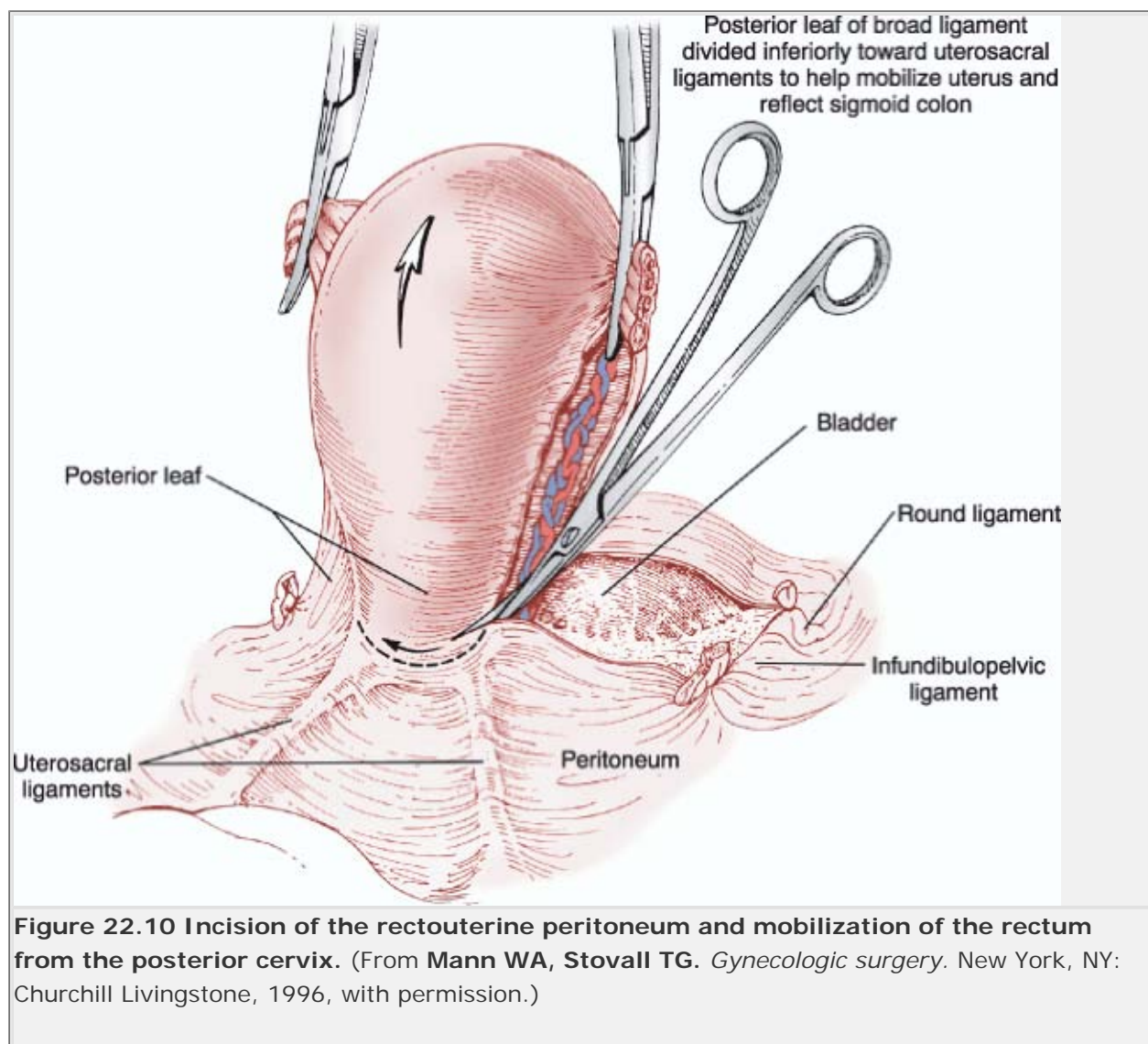
Bowel Injury

Small bowel injuries are the most common intestinal injuries in gynecologic surgery (89). Small defects of the serosa or muscularis may be repaired using a single layer of continuous

or interrupted 3–0 braided absorbable suture. Although single-layer closure of the small bowel has proved adequate, it is safer to close defects involving the lumen in two layers using a 3–0 braided absorbable suture. **The defect should be closed in a direction perpendicular to the intestinal lumen.** If a large area has been injured, resection with reanastomosis may be necessary (88,90). Because the bacterial flora of the ascending colon is similar to that of the small bowel, injuries can be repaired in a similar manner. The transverse colon rarely is injured in normal gynecologic procedures because it is well outside the operative field. However, the descending colon and the rectosigmoid colon are intimately involved with the pelvic structures and are at significant risk for injury during gynecologic surgery. Injuries not involving the

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mucosa may be repaired with a single running layer of 2–0 or 3–0 braided absorbable suture. If the laceration involves the mucosa, it may be closed as with small bowel injuries if the colon has been prepared adequately. Otherwise, diverting colostomy may be necessary in some patients to protect the repair site from fecal contamination, especially if the defect is larger than 5 cm or if there is spillage of the bowel contents (88,90).



Hemorrhage

Significant arterial bleeding usually arises from the uterine arteries or the ovarian vessels near the insertion of the infundibulopelvic ligaments (91). Blind clamping of

these vessels presents a risk for ureteral injury; therefore, the ureters should be identified in the retroperitoneal space and traced to the area of bleeding to avoid inadvertent ligation. **It is best to apply a pressure pack to tamponade the bleeding and then slowly remove the pack in an effort to visualize, isolate, and individually clamp the bleeding vessels.** Mass ligatures should be avoided. The use of surgical clips may be helpful. Venous bleeding is less dramatic but often is more difficult to manage, particularly in the presence of extensive adhesions and fibroids. This type of bleeding can be controlled with pressure alone or with suture ligation. Bleeding from peritoneal edges or denuded surfaces may be controlled with pressure, application of topical agents such as thrombin or collagen, or Bovie cautery. A variety of laser techniques have been used to control bleeding.

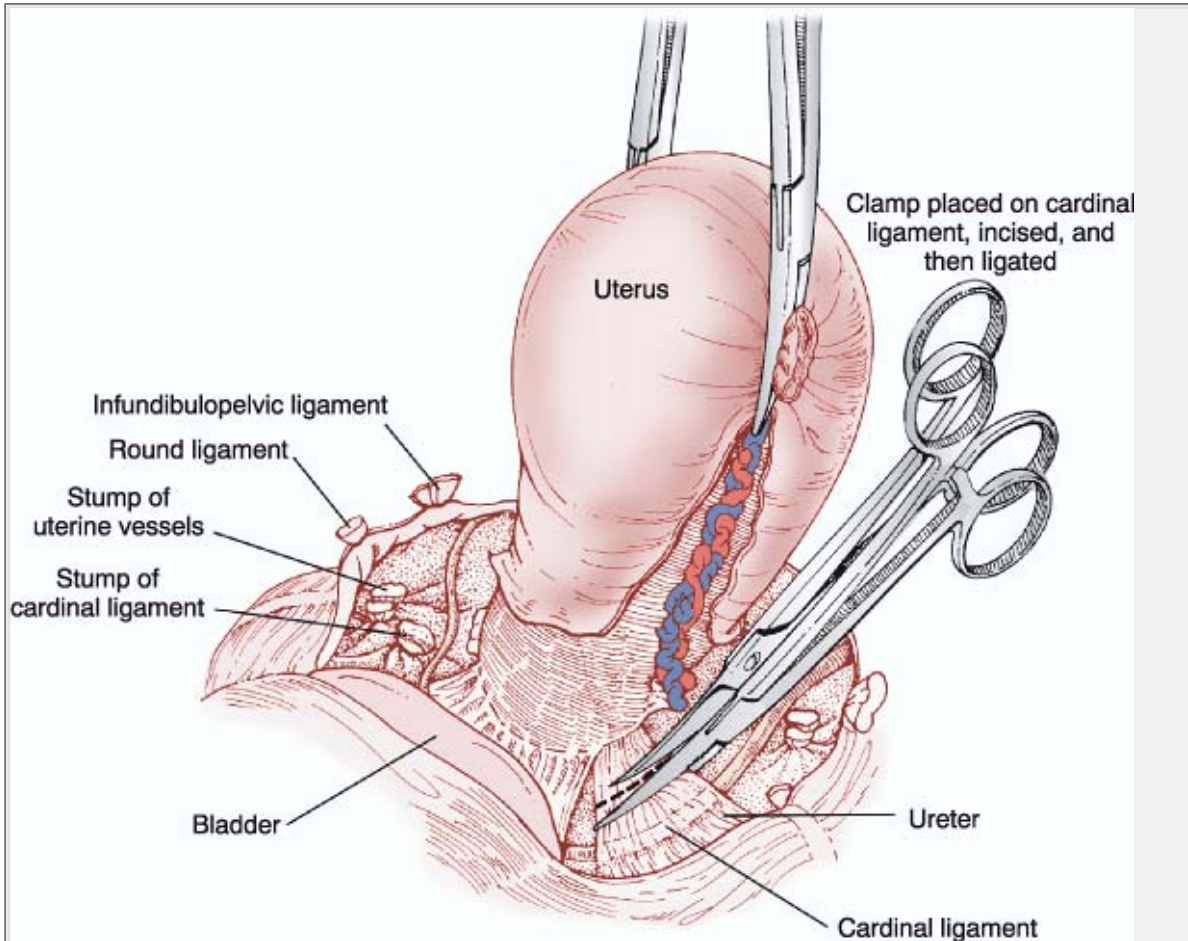


Figure 22.11 Ligation of the cardinal ligament. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

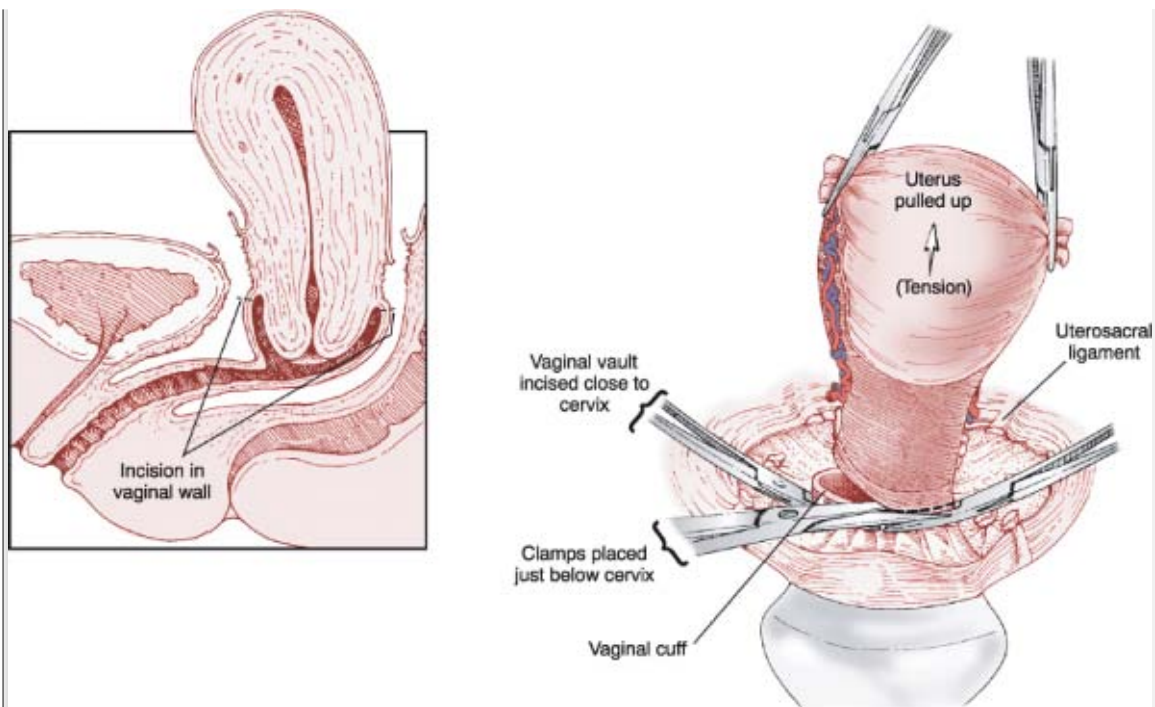


Figure 22.12 Removal of the uterus by transection of the vagina. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996.)

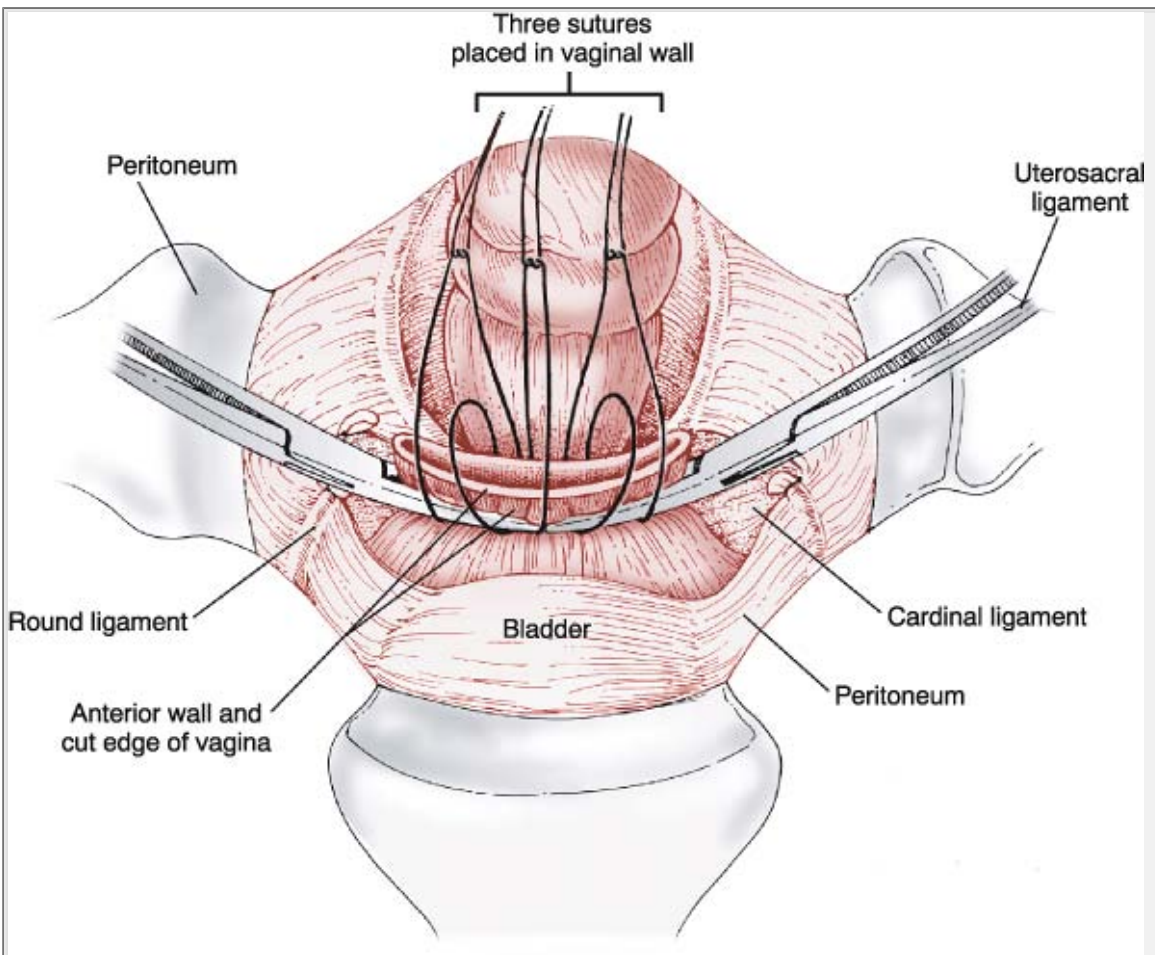


Figure 22.13 Vaginal cuff closure incorporating the uterosacral and cardinal ligaments. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

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Postoperative Management

Bladder Drainage

Overdistention of the bladder resulting from bladder trauma or the patient's reluctance to initiate the voluntary phase of voiding is one of the most common complications after abdominal hysterectomy (92). For this reason, an indwelling bladder catheter should be used for the first few postoperative hours until the patient is able to ambulate and urinate.

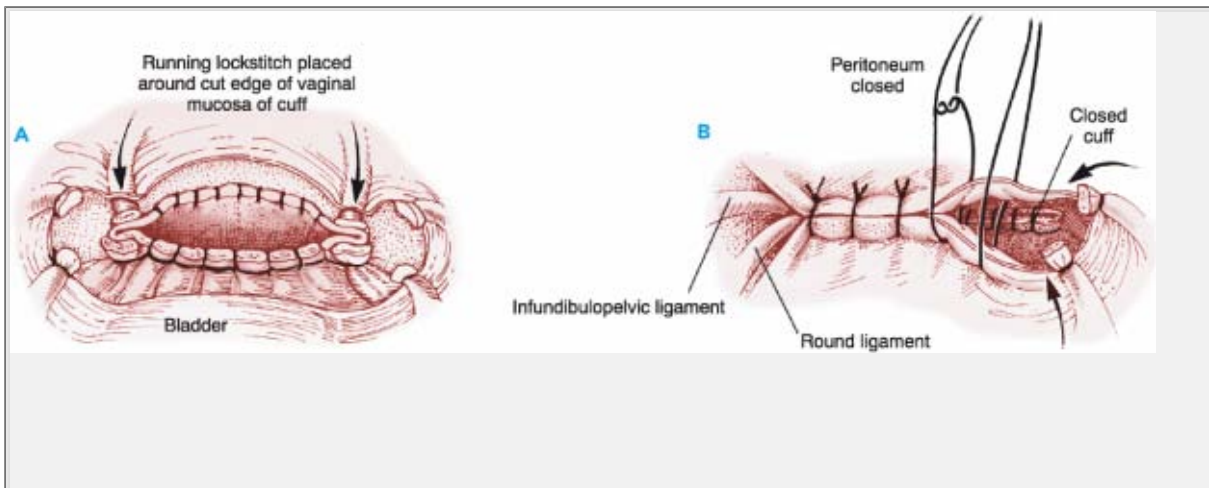


Figure 22.14 A: Vaginal cuff left open with a running suture along the cuff. B: Peritoneum closed. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

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If retropubic urethropexy has been performed, consideration should be given to using a suprapubic catheter, which allows postvoid residual levels to be checked without repetitive catheterizations. This catheter may be removed when satisfactory postvoid residual levels of less than 100 mL have been obtained.

Diet

In anticipation of the rare case in which the patient must be returned to the operating room, the patient is allowed only ice chips and liquids on the day of surgery. On the first postoperative day, assuming bowel sounds are present, diet is resumed, advancing to solid foods as tolerated. This dietary regimen assumes minimal intraoperative bowel manipulation and dissection.

Early postoperative feeding has been shown not only to be safe but also to speed return of bowel function and recovery. In patients who have undergone pelvic and para-aortic lymphadenectomy, bowel surgery, or other extensive dissections, a slower return to normal bowel function may occur, so care should be taken to advance the diet only as tolerated.

Activity

Early ambulation decreases the incidence of thrombophlebitis and pneumonia. Patients are encouraged to begin ambulation on their first postoperative day if possible and to increase their time out of bed progressively as their strength improves. **On discharge, the patient is instructed to avoid lifting more than 20 pounds for 6 weeks, thereby minimizing stress on fascia to allow full healing. Sexual intercourse is not recommended until 6 weeks after surgery, when the vaginal cuff is fully healed.** Patients are instructed to avoid driving until full mobility returns because postoperative pain and tenderness may hinder sudden braking or steering maneuvers in emergency situations. With these exceptions, the patient is encouraged to return to normal activities as soon as she feels comfortable doing so.

Wound Care

The abdominal incision normally requires little attention, except for ordinary hygienic measures. The wound is kept covered with a sterile bandage for the first 24 hours after surgery, by which time the incision has sealed. After the bandage has been removed, the incision should be cleaned daily with mild soap and water and kept dry.

Vaginal Hysterectomy

Preoperative Evaluation

Evaluation of Pelvic Support

The most important observation in determining the feasibility of a vaginal hysterectomy is the demonstration of uterine mobility (92,93). A vaginal approach should not be chosen if the uterus is not freely mobile. Pelvic support structures are elevated at the initial pelvic examination. In patients with no apparent prolapse, poor pelvic support can often be demonstrated by observing descent of the uterus with a series of Valsalva maneuvers. Although vaginal hysterectomy is easier to perform when the uterine supporting ligaments are lax, it is not an absolute requirement. Some gynecologists advocate the application of a tenaculum to the anterior cervical lip, with subsequent traction applied as the patient bears down. Although this exercise may give some indication of uterine mobility, it is uncomfortable and not necessarily predictive of the success of vaginal hysterectomy. Therefore, **the practice of applying traction to the cervix with a tenaculum to demonstrate descent of an apparently well-supported uterus is not recommended.**

Evaluation of the Pelvis

After assessment of pelvic support, the bony pelvis should be evaluated. Ideally, the angle of the pubic arch should be 90 degrees or greater, the vaginal canal should be ample, and the posterior vaginal fornix should be wide and deep. The surgeon may use a closed fist to approximate the bituberous diameter, which should

exceed 10 cm. The size and shape of the female pelvis contributes to increased exposure. The importance of a wide pubic arch was underscored by the result of a study of 25 failed vaginal hysterectomies that were compared with 50 successful vaginal hysterectomies. Risk factors, such as age, parity, body weight, surgical indication, uterine size, presence of

leiomyomata in the anterior lower uterine segment, previous pelvic surgeries, adhesions, location and length of the cervix, and narrow pubic arch (less than 90 degrees), were examined. In the study, only the presence of a narrow pubic arch increased the risk of vaginal hysterectomy (94).

Surgical Considerations

Patient Positioning

Once the patient is in the dorsal lithotomy position, the buttocks should be positioned just over the table's edge. Several stirrup types are available, including those that support the entire leg and those that suspend the legs in straps. **To avoid nerve injury, adequate padding should be used; marked flexion of the thigh and pressure points should be avoided.**

Trendelenburg (10- to 15-degree) positioning aids in the intravaginal visualization needed during surgery.

Vaginal Preparation

A povidone-iodine solution is applied to the vagina, the bladder is drained, and the catheter is removed. Several methods for draping have been proposed, including individual or single-piece drapes; the method chosen is at the surgeon's discretion. There is usually no need to shave or clip the pubic hair. Individual drapes with an adhesive barrier should be used to hold the drapes in place and prevent the pubic hair from compromising the field.

Instruments

Instruments specific to and useful in performing a vaginal hysterectomy include right-angled retractors, narrow Deaver retractors, weighted specula, Heaney needle holders, and an assortment of Briesky-Navratil vaginal retractors. Heaney and Heaney-Ballentine hysterectomy clamps are preferable. Several other clamps also are commonly used, including the Masterson clamp.

Lighting

Overhead high-intensity lamps should be used and positioned to direct light over the operator's shoulder. In addition, the surgeon may prefer a headlight, which can be worn to provide direct horizontal lighting. Although not routinely used, a fiberoptic-lighted irrigating suction system can provide additional light and transilluminate tissue planes.

Suture Material

Various suture materials have been advocated for gynecologic surgery. The type of suture material chosen should be based on the surgeon's preference. A synthetic delayed absorbable polyglactin or polyglycolic acid suture and atraumatic needles are generally preferable.

Procedure

The patient is examined while anesthetized to confirm prior findings and to assess uterine mobility and descent. The decision is then made whether to proceed vaginally or abdominally.

Grasping and Circumscribing the Cervix

The anterior and posterior lips of the cervix are grasped with a single- or double-toothed tenaculum. With downward traction applied on the cervix, a circumferential incision is made in the vaginal epithelium at the junction of the cervix (Fig. 22.15).

Dissection of Vaginal Mucosa

After the initial incision is made, the vaginal epithelium may be dissected sharply from the underlying tissue or pushed bluntly with an open sponge (Fig. 22.16). **If the initial incision is made too close to the external cervical os,**

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there is a greater amount of dissection required and associated bleeding. Therefore, this circumscribing incision should be made just below the bladder reflection. It is important to continue the dissection in the correct cleavage plane because dissection in the wrong plane will increase blood loss.

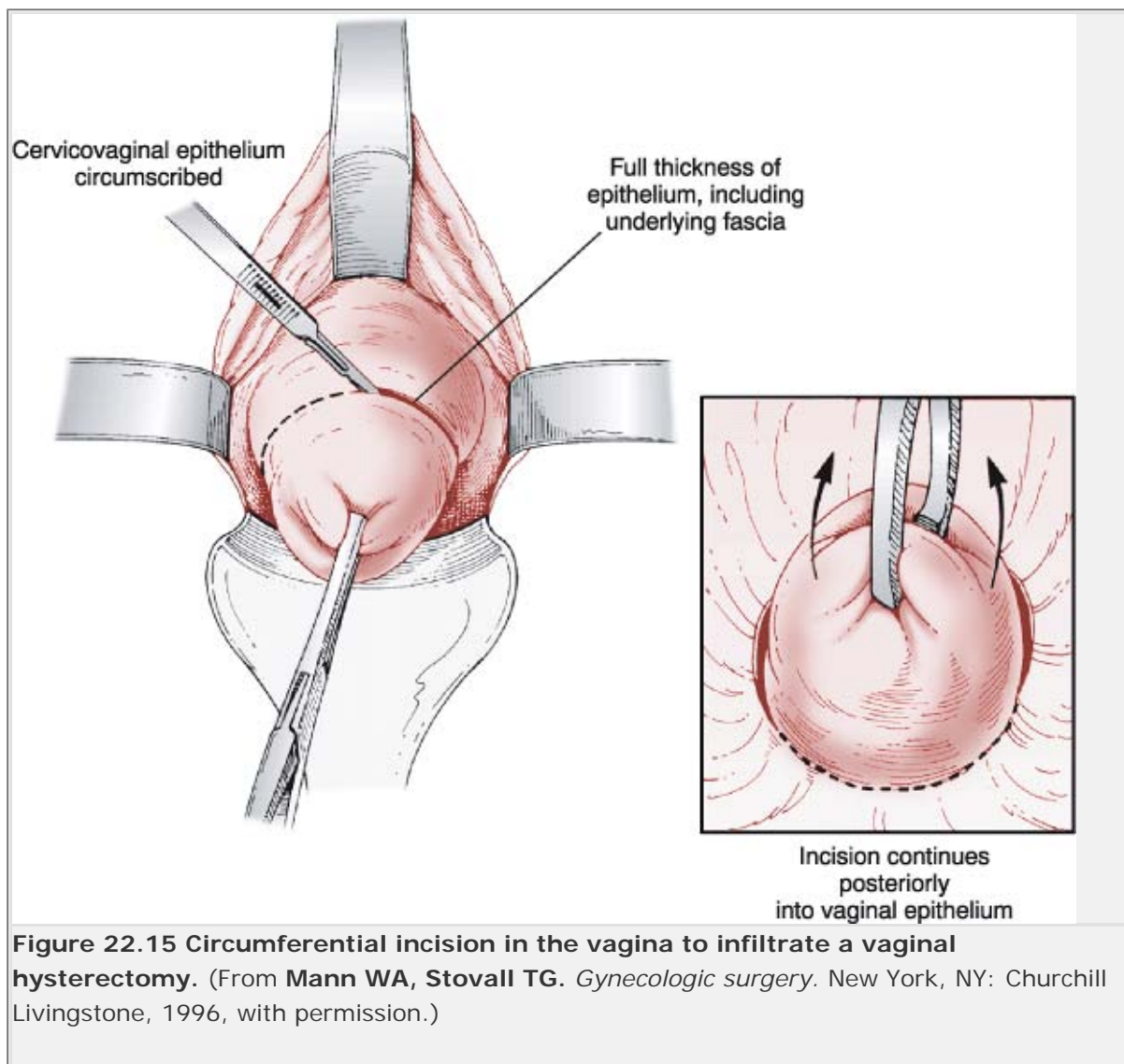


Figure 22.15 Circumferential incision in the vagina to infiltrate a vaginal hysterectomy. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

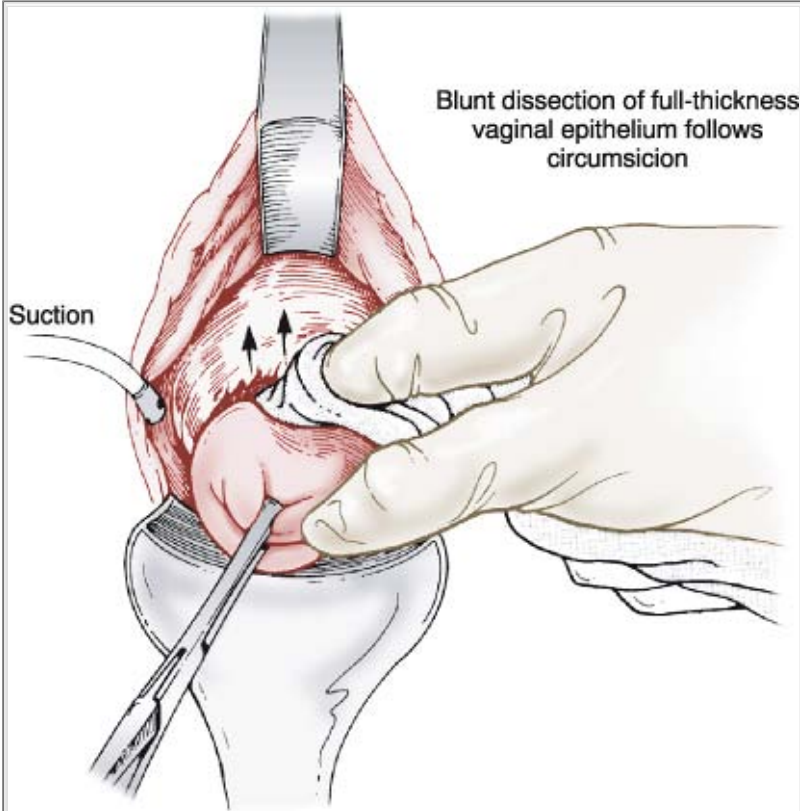


Figure 22.16 Dissection of the vaginal mucosa. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

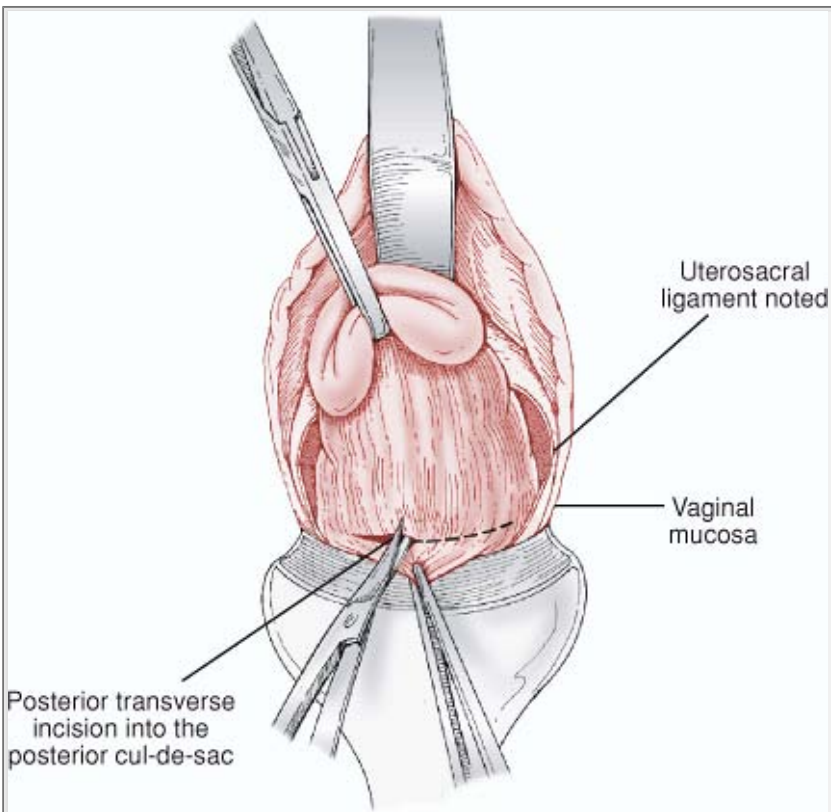


Figure 22.17 Entry into the posterior cul-de-sac. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Posterior Cul-de-Sac Entry

The peritoneal reflection of the posterior cul-de-sac (cul-de-sac of Douglas) can be identified by stretching the vaginal mucosa and underlying connective tissue with forceps (Fig. 22.17). If difficulty is encountered (e.g., if the cervix is elongated and the peritoneum is not evident), the vaginal mucosa may be incised vertically to the point at which the cul-de-sac becomes more apparent.

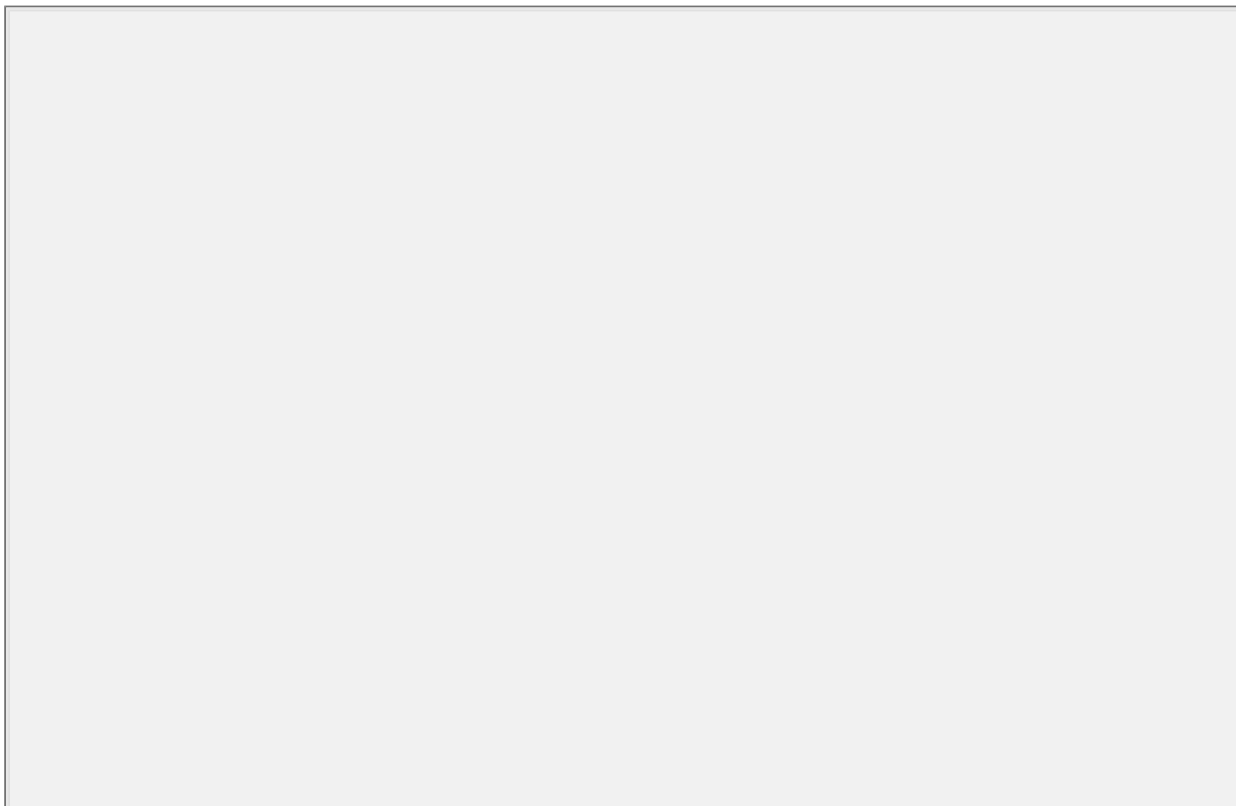
If the vaginal mucosa has been dissected in the wrong plane, the hysterectomy may be begun extraperitoneally by clamping and cutting the uterosacral and cardinal ligaments close to the cervix. The posterior cul-de-sac will then become readily identifiable. If the peritoneal reflection of the posterior cul-de-sac still cannot be identified, entry into the anterior peritoneum is attempted, and a finger is hooked into the posterior cul-de-sac to place tension on the peritoneum. The peritoneum is opened with Mayo scissors. An interrupted suture is placed to approximate the peritoneum and vaginal cuff and thus provide hemostasis (Fig. 22.18). The posterior pelvic cavity is examined for pathologic alterations of the uterus or adhesive disease of the cul-de-sac. The weighted speculum is placed into the posterior cul-de-sac.

Uterosacral Ligament Ligation

With retraction of the lateral vaginal wall and countertraction on the cervix, the uterosacral ligaments are clamped with the tip of the clamp incorporating the lower portion of the cardinal ligaments (Fig. 22.19). The clamp is placed perpendicular to the uterine axis, and the pedicle is cut close to the clamp and sutured. A small pedicle (0.5 cm) distal to the clamp is optimal because a larger pedicle becomes necrotic and the tissue sloughs, which may become culture medium for micro-organisms.

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The pedicle should be incised no more than one half to three fourths of the way around the tip of the clamp. Limiting the incision prevents the next pedicle, which may be vascular, from being cut.



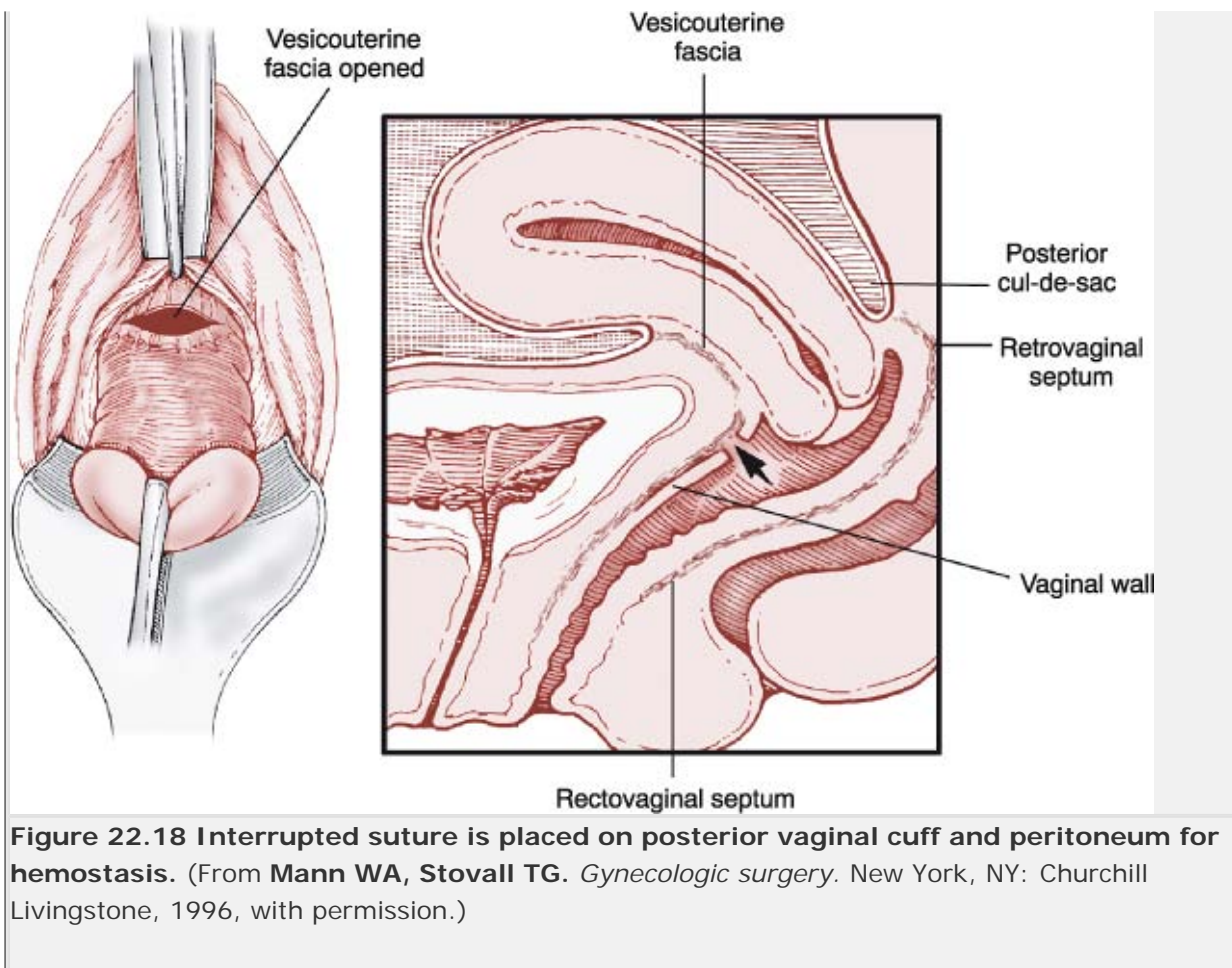


Figure 22.18 Interrupted suture is placed on posterior vaginal cuff and peritoneum for hemostasis. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

When suturing any pedicle, the needle point is placed at the tip of the clamp, and the needle is passed through the tissue by a rolling motion of the operator's wrist. Once

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ligated, the uterosacral ligaments may be transfixed to the posterolateral vaginal mucosa (Fig. 22.20). This suture may lend additional support to the vagina and provides hemostasis at this point on the vaginal mucosa. This suture is held with a hemostat to facilitate location of any bleeding at the completion of the procedure and to aid in the closure of vaginal mucosa.

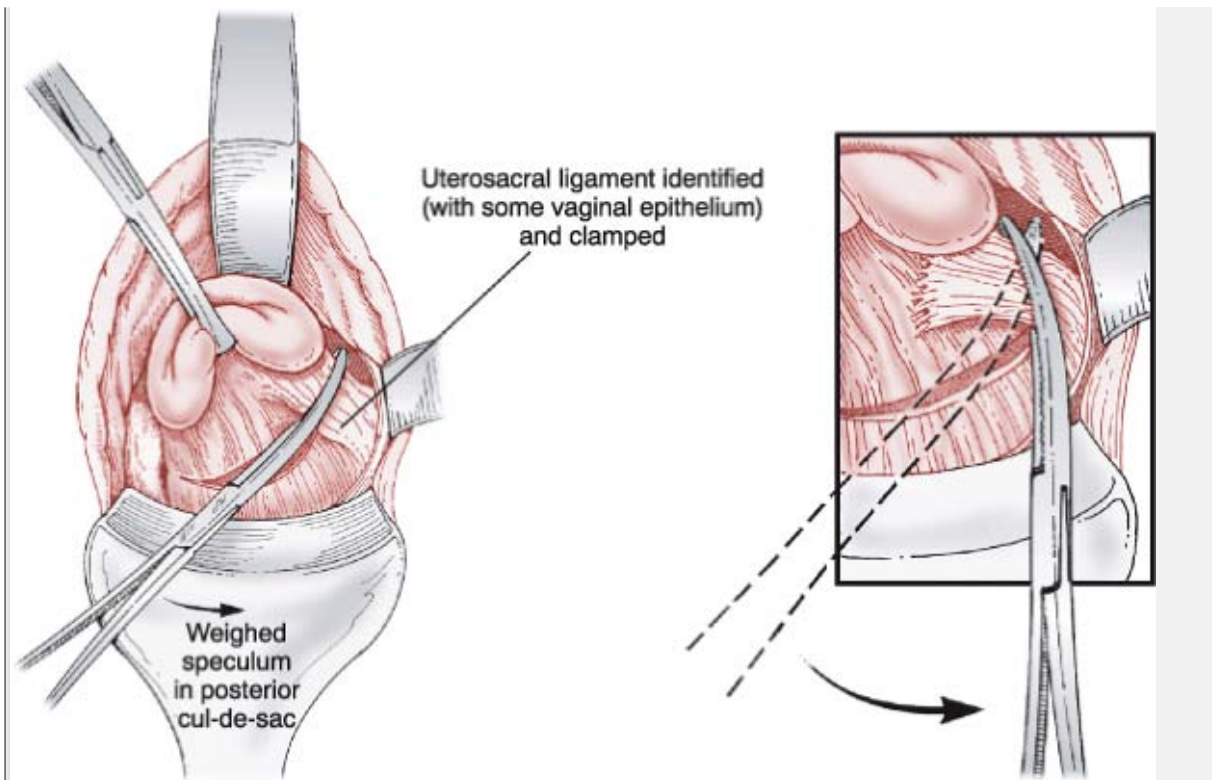


Figure 22.19 Ligation of the uterosacral ligaments. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

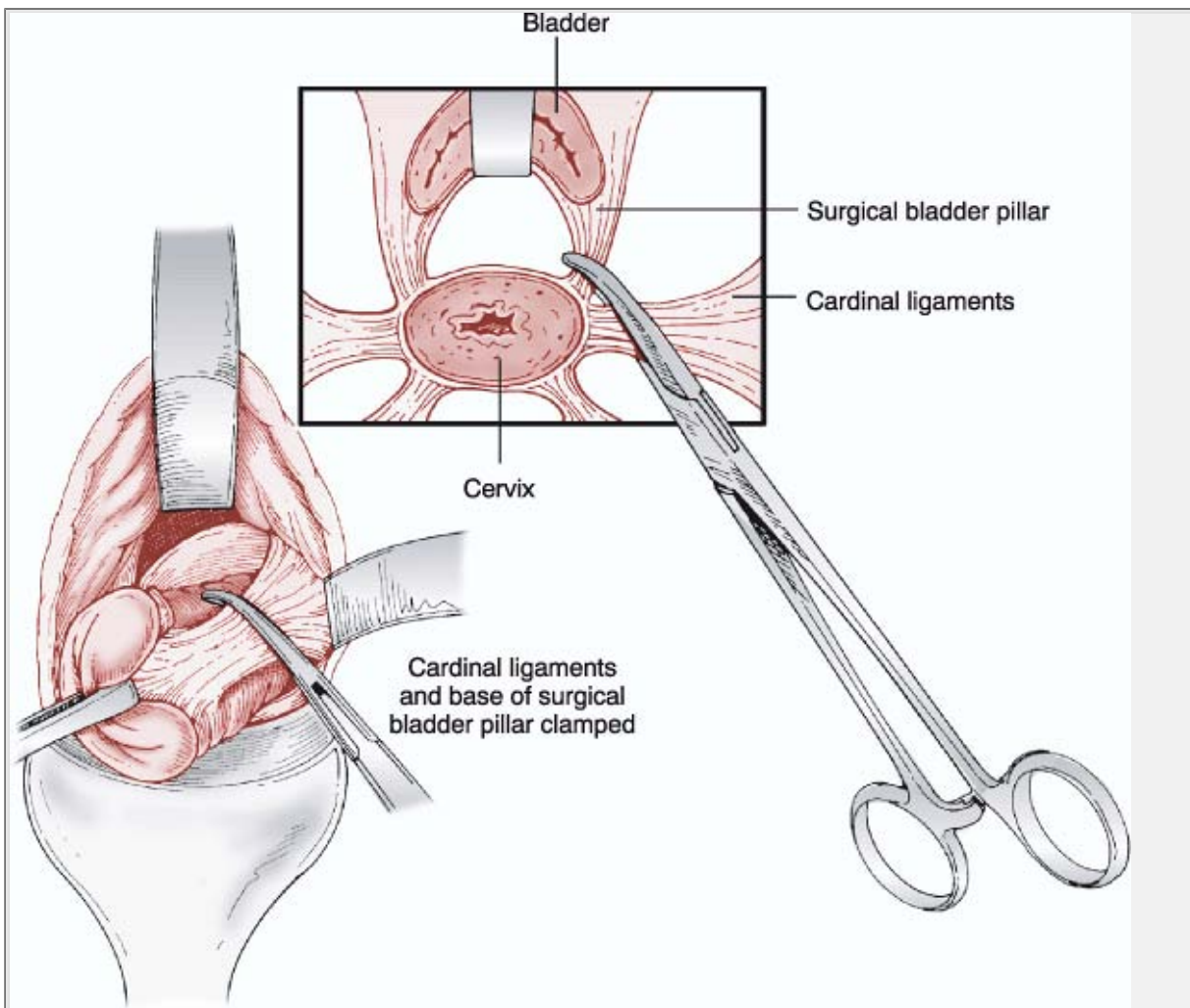


Figure 22.20 Transfixion of the uterosacral ligament to the posterolateral vaginal mucosa. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Entry versus Nonentry into the Vesicovaginal Space (Cul-de-Sac)

Downward traction is placed on the cervix. Using either Mayo scissors, with the points directed toward the uterus, or an open moistened 4 × 4 gauze sponge, the bladder is advanced. If the vesico-vaginal peritoneal reflection is easily identified at this point, the vesicovaginal space may be entered. Otherwise, it may be preferable to delay entry. There is no danger in delaying entry so long as the operator has ascertained that the bladder has been advanced.

After the bladder has been advanced, a curved Deaver or Heaney retractor is placed in the midline, holding the bladder out of the operative field. This process precedes each step of the vaginal hysterectomy until the vesicovaginal space is entered.

Cardinal Ligament Ligation

With traction on the cervix continued, the cardinal ligaments are identified, clamped, and cut. The suture is ligated (Fig. 22.21).

Advancement of Bladder

The bladder again is advanced out of the operative field. A blunt dissection technique may be used; however, sharp dissection may be helpful if the patient has had previous surgery, such as cesarean delivery, which may have scarred the bladder reflection.

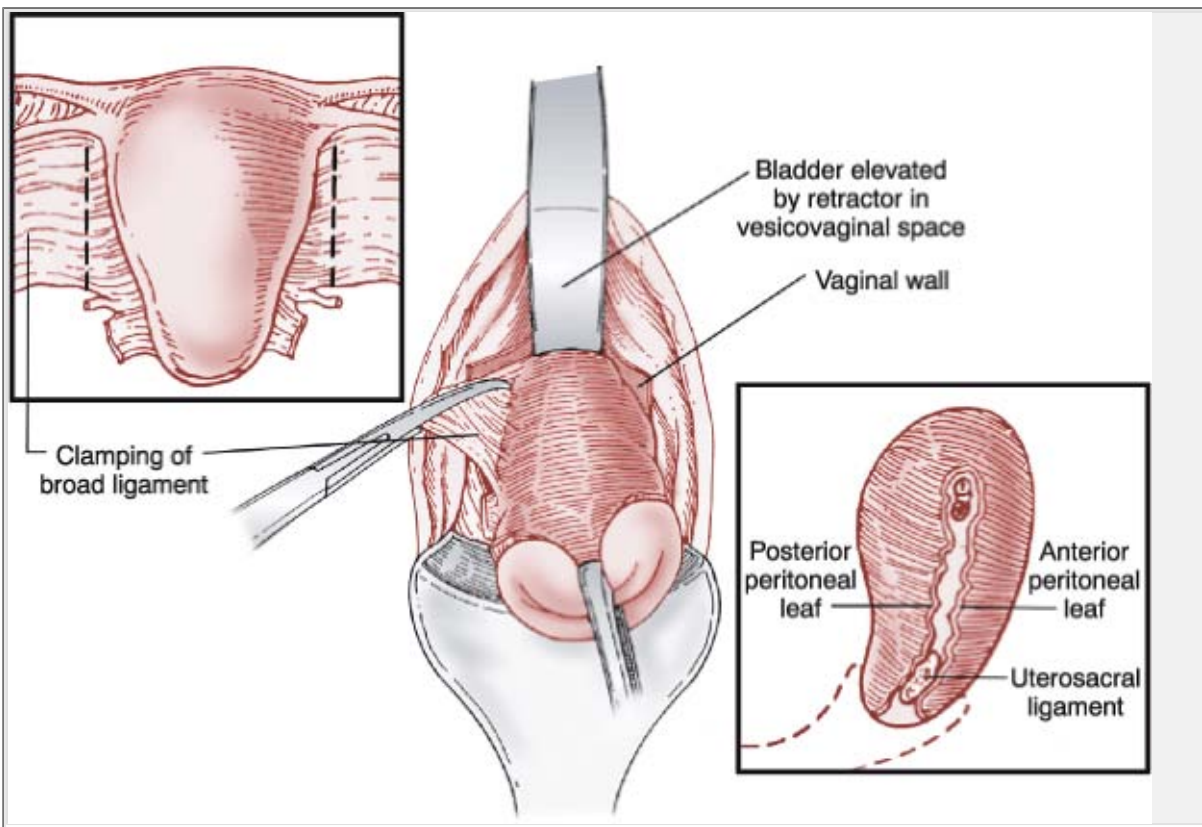


Figure 22.21 Ligation of the cardinal ligament. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

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Uterine Artery Ligation

Contralateral and downward traction is placed on the cervix. **With an effort to incorporate the anterior and posterior leaves of the visceral peritoneum, the uterine vessels are identified, clamped, and cut, and the suture is ligated** (Fig. 22.22). **A single suture and single clamp technique is adequate and decreases the potential risk for ureteral injury.** When the uterus is large or when a fibroid distorts the

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anatomic relationships, a second suture may be required to ligate any remaining branches of the uterine artery.

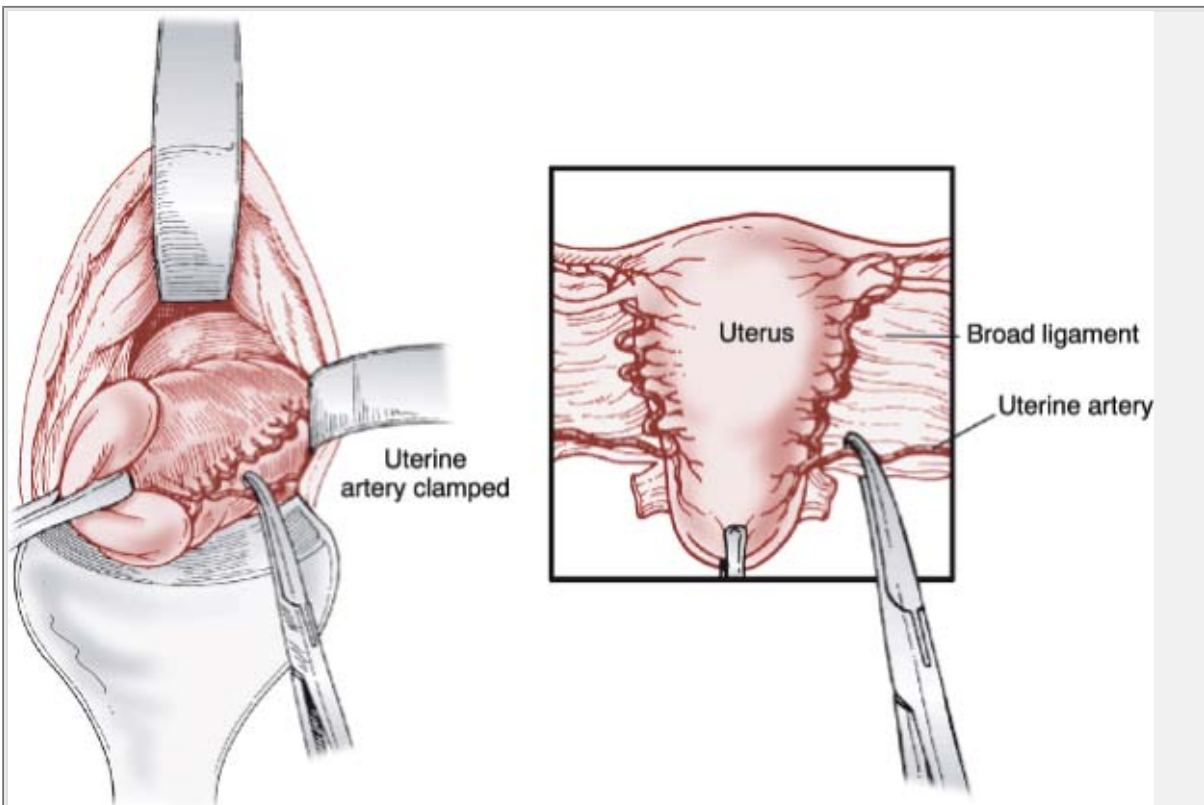


Figure 22.22 Ligation of the uterine artery. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996.)

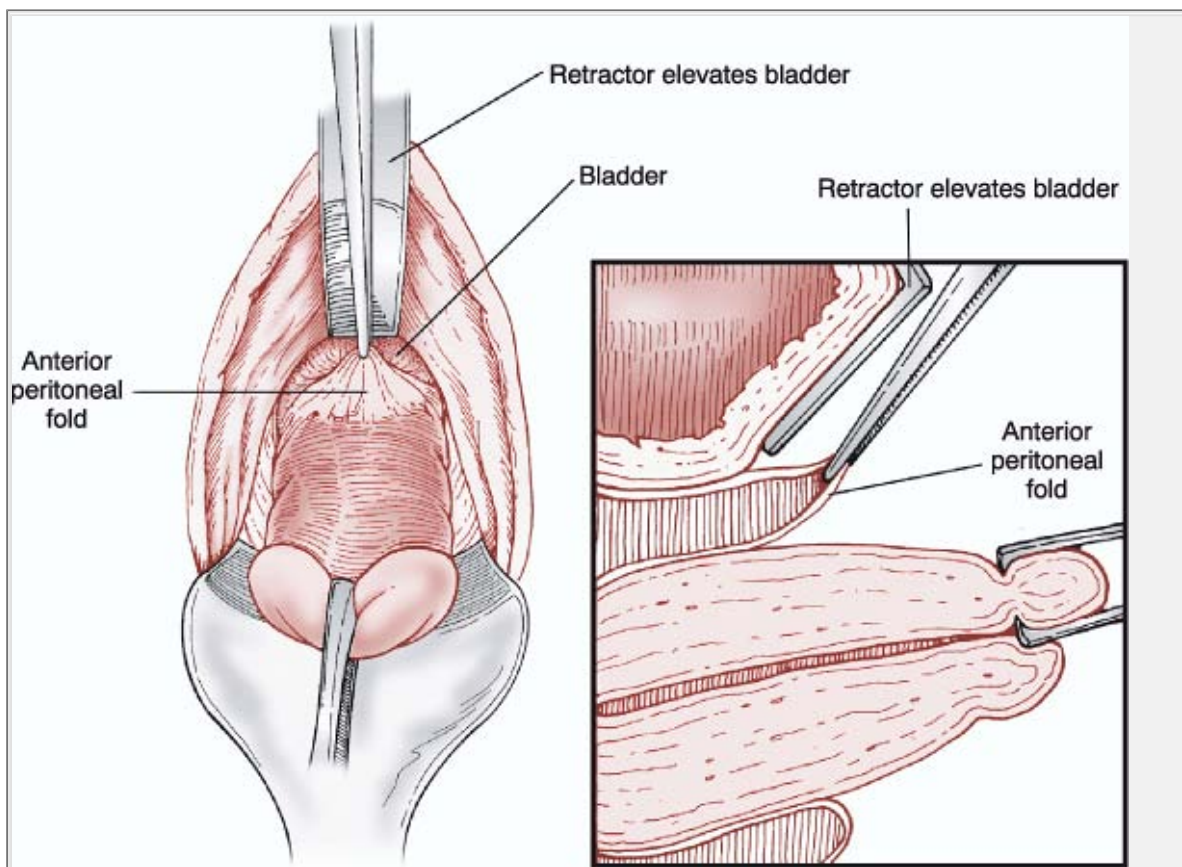


Figure 22.23 Entry into the vesicovaginal space. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Entry into the Vesicovaginal Space

The anterior peritoneal fold usually can be identified readily just before or after clamping and suture ligation of the uterine arteries. The anterior peritoneal cavity should not be opened blindly because of the increased risk of bladder injury (Fig. 22.23). The peritoneum is grasped with forceps, tented, and opened with scissors with the tips pointed toward the uterus. A Heaney or Deaver retractor is then placed, and the peritoneal contents are identified. This retractor serves to keep the bladder out of the operative field.

Delivery of the Uterus

A tenaculum is placed onto the uterine fundus in a successive fashion to deliver the fundus posteriorly (Fig. 22.24). The operator's index finger is used to identify the utero-ovarian ligament and aid in clamp placement.

Utero-ovarian and Round Ligament Ligation

With the posterior and anterior peritoneum opened, the remainder of the broad ligament and utero-ovarian ligaments are clamped, cut, and ligated (Fig. 22.25). The utero-ovarian and round ligament complexes are double ligated with a suture tie followed by a ligature medial to the first suture. A hemostat is placed on the second suture to aid in the identification of any bleeding and to assist with peritoneal closure. A hemostat should not be placed on the first suture or any other vascular pedicle to avoid the risk for loosening the tie.

Removal of the Ovaries

When the adnexa are removed, the round ligaments should be removed separately from the adnexal pedicles. Traction is placed on the utero-ovarian pedicle. The ovary is drawn into the operative field by grasping it with a Babcock clamp. A Heaney clamp is placed across the infundibulopelvic ligament, and the ovary and tube are excised (Fig. 22.26). A transfixion tie and suture ligation are placed on the infundibulopelvic ligament. The surgeon should not be reluctant to remove the fallopian

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tube separately from the ovary if taking them together risks loss of the tissue pedicle or injury to the ureter or nearby blood vessels.

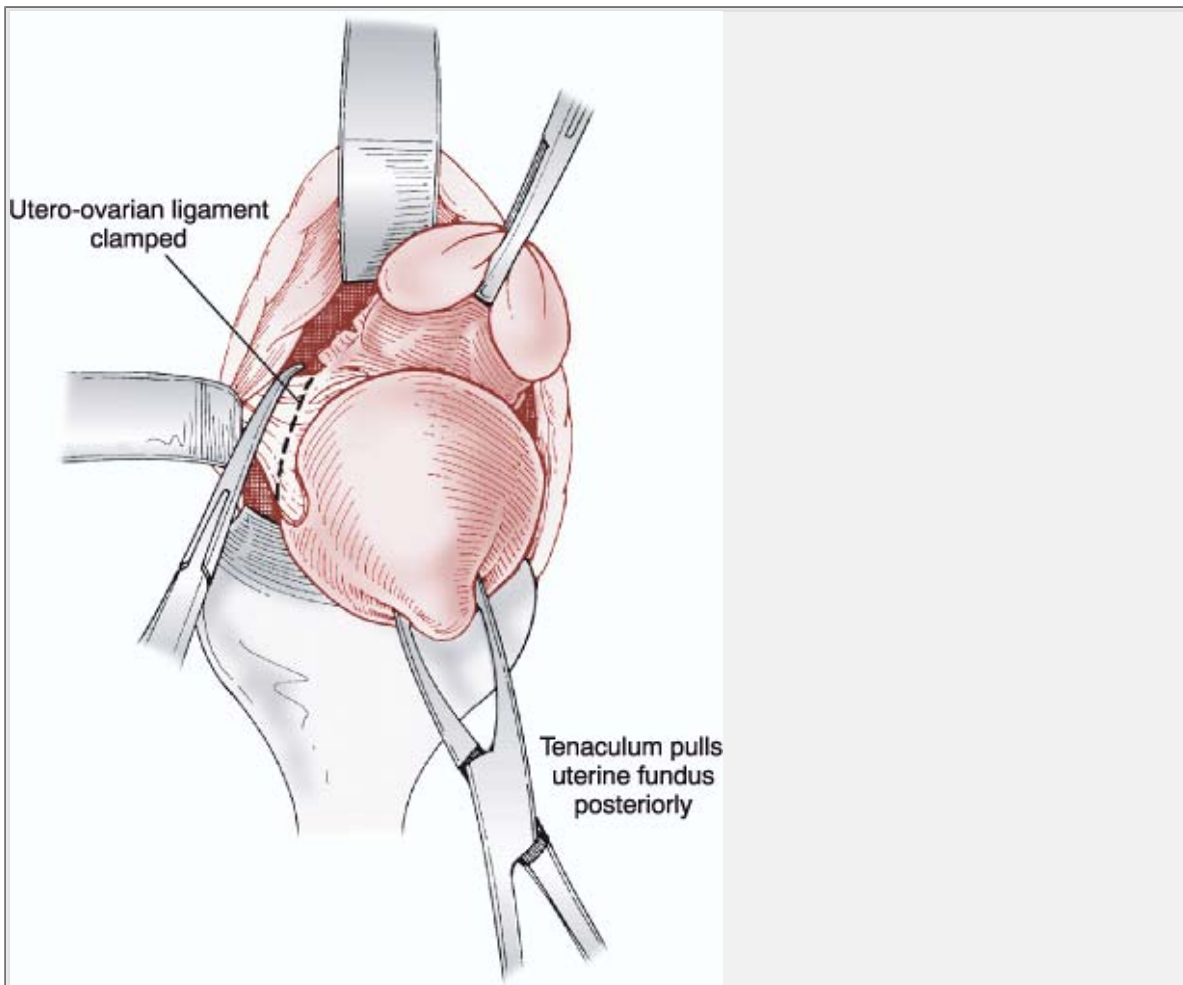


Figure 22.24 Delivery of the uterine fundus posteriorly. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

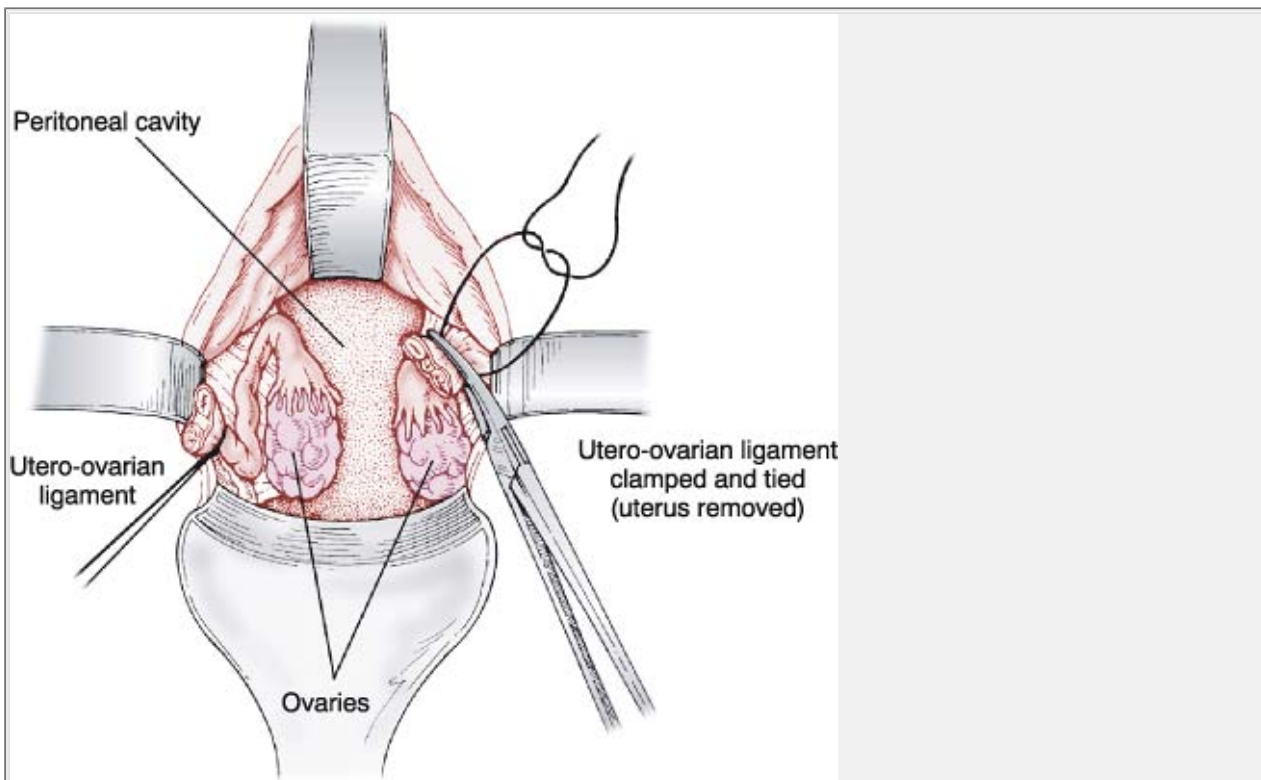


Figure 22.25 Ligation of the utero-ovarian and round ligaments. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

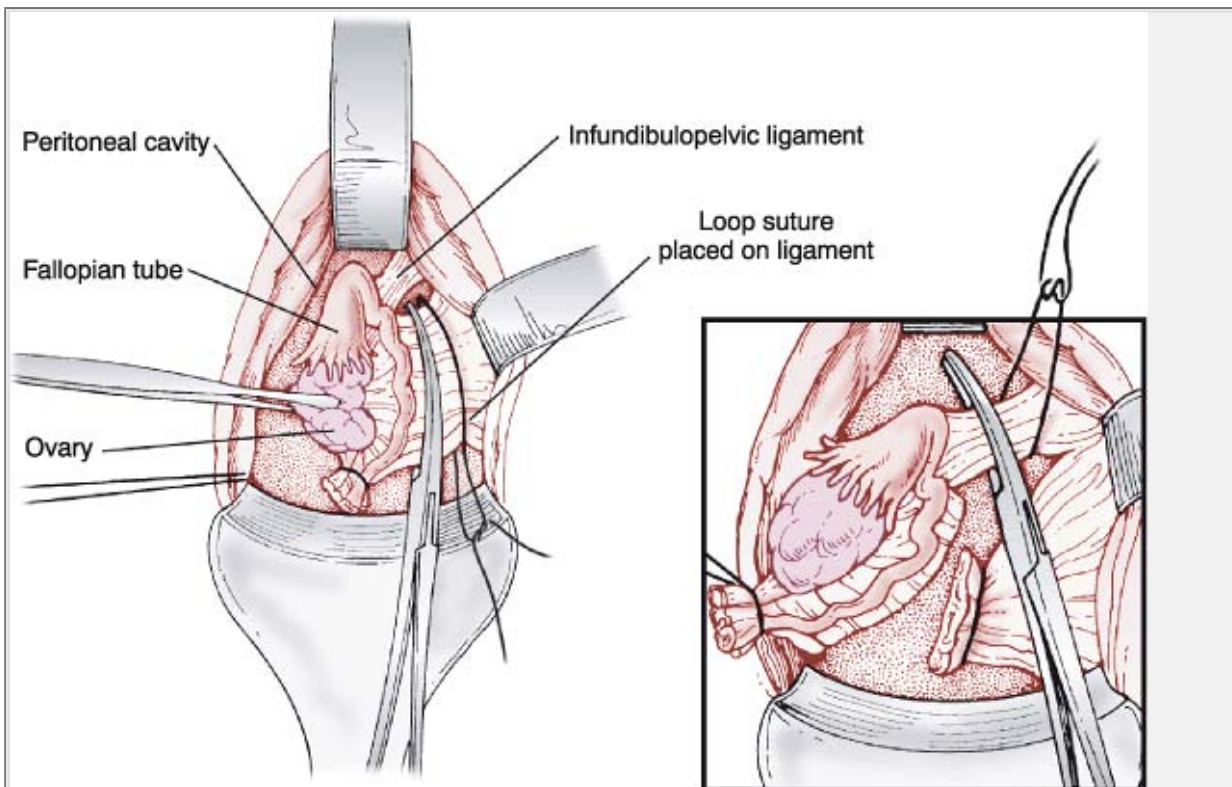


Figure 22.26 Removal of the ovaries and fallopian tubes by clamping across the infundibulopelvic ligament. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Hemostasis

A retractor or tagged sponge is placed into the peritoneal cavity, and each of the pedicles is visualized and inspected for hemostasis. If additional sutures are required, they should be placed precisely with care to avoid the ureter or bladder.

Peritoneal Closure

Because the pelvic peritoneum does not provide support and re-forms in 24 hours after surgery, the peritoneum need not be reapproximated routinely. If it is believed to be important, the anterior peritoneal edge is identified and grasped with forceps. A continuous absorbable 0-0 suture is begun at the 12-o'clock position. The suture is continued in a purse-string fashion and incorporates the distal portion of the left upper pedicle and the left uterosacral ligament (Fig. 22.27). Tension is applied to the suture placed at the beginning of the procedure that incorporates the posterior peritoneum and vaginal mucosa. This allows for high posterior reperitonealization, which shortens the cul-de-sac and thus helps to prevent future enterocele formation. The right uterosacral ligament and the distal portion of the right upper pedicle are incorporated, and this continuous suture ends at the point on the anterior peritoneum where it was begun.

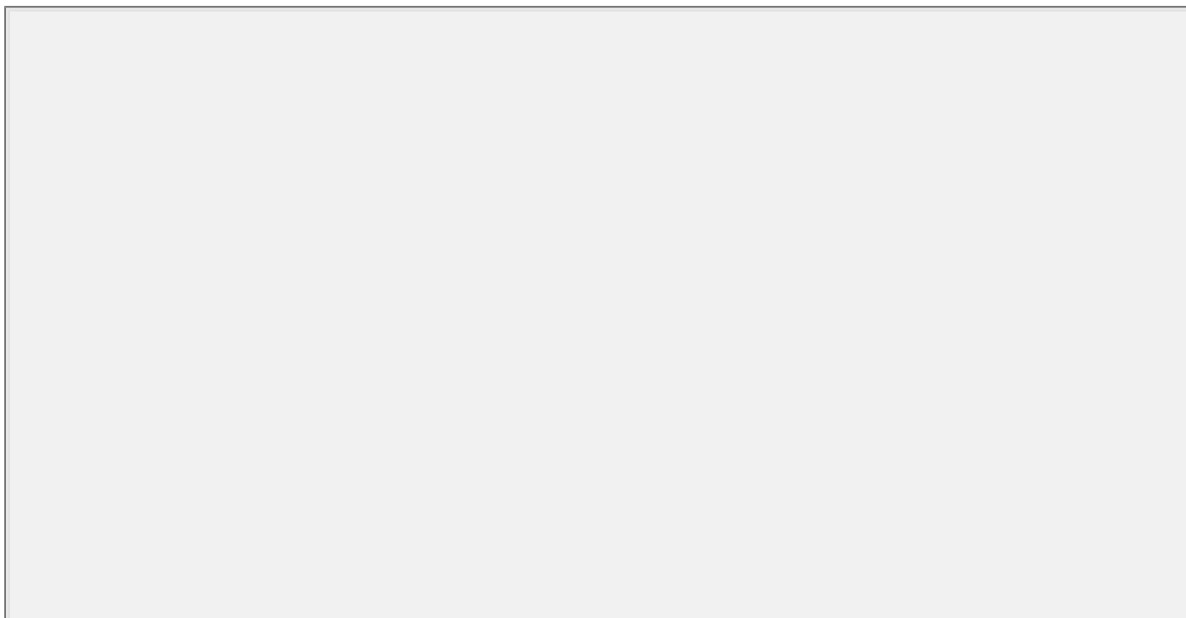
The intra-abdominal tagged sponge is removed and inspected for the presence of blood at its distal end. The slack of the purse-string peritoneal suture is taken up by pulling the suture tight. Before tying the peritoneal suture, the surgeon should make certain that no prolapse of viscera has occurred.

Vaginal Mucosa Closure

The vaginal mucosa can be reapproximated in a vertical or horizontal manner, using either interrupted or continuous sutures (Fig. 22.28). The vaginal mucosa is, in this case, reapproximated horizontally with interrupted absorbable sutures. The sutures are placed through the entire thickness of the vaginal epithelium, with care taken to avoid entering the bladder anteriorly. These sutures will obliterate

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the underlying dead space and produce an anatomic approximation of the vaginal epithelium, thereby decreasing the postoperative formation of granulation tissue.



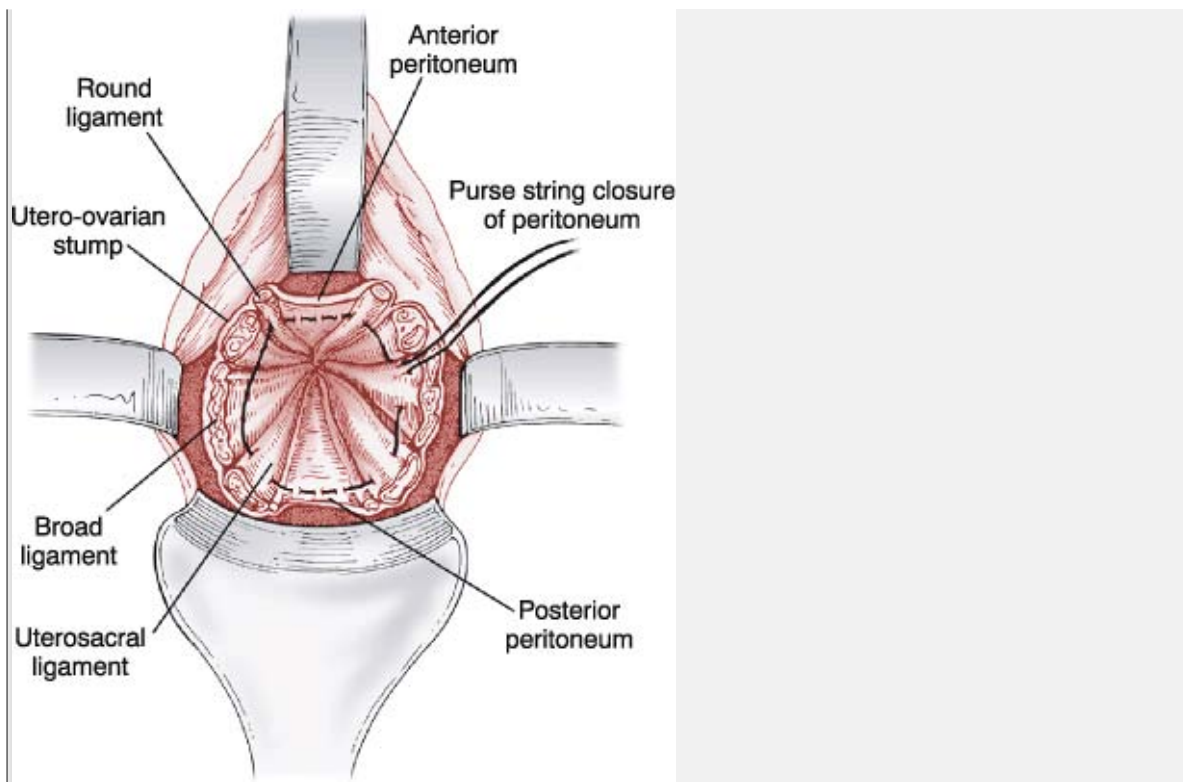


Figure 22.27 Closure of the peritoneum. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Bladder Drainage

After completion of the procedure, the bladder is drained. Unless an anterior or posterior colporrhaphy or other reconstructive procedure is performed, neither bladder catheter nor vaginal packing are mandatory.

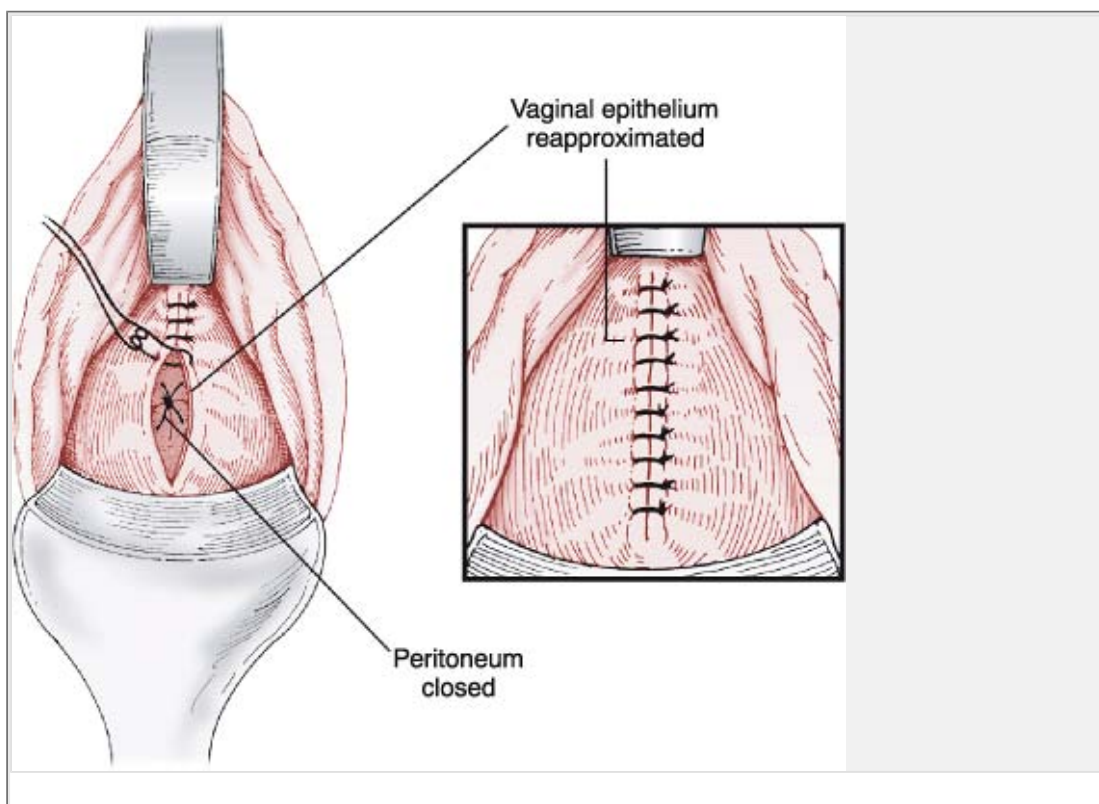


Figure 22.28 Closure of the vaginal mucosa. (From Mann WA, Stovall TG. *Gynecologic surgery*. New York, NY: Churchill Livingstone, 1996, with permission.)

Surgical Techniques for Selected Patients

Injection of Vaginal Mucosa

The use of paracervical and submucosal injection of 20 to 30 mL of 0.5% lidocaine with 1:200,000 epinephrine before incision of the vaginal mucosa is believed by some to decrease postoperative pain and facilitate identification of surgical planes. There is no need to inject the cervix. Areas to be injected include the bladder pillars, lower portion of the cardinal ligament, uterosacral ligaments, and paracervical tissue. However, it has been shown that the incidence of cuff cellulitis and cuff abscess formation is increased when *epinephrine* is injected into the cervicovaginal mucosa.

Morcellation of the Large Uterus

Uterine morcellation is a well known but often underutilized surgical procedure whereby the uterus is removed piecemeal. Several methods of uterine morcellation have been described (95), including hemisection or bivalving, wedge or "V" incisions, and intramyometrial coring. Before beginning any morcellation procedure, the uterine vessels must be ligated, and the peritoneal cavity must be entered. When uterine hemisection or bivalving is performed, the cervix is split at the midline, and the uterus is cut into halves, which are removed separately (96,97). This method seems best suited for fundal, midline leiomyomas.

Wedge morcellation is best suited for anterior or posterior fibroids or for fibroids in the other broad ligaments (i.e., when the fibroids are away from the midline) (97,98,99,100,101). The cervix is amputated, and the myometrium is grasped with clamps. Wedge-shaped portions of myometrium are removed from the anterior or posterior uterine wall. The apex of the wedge is kept in the midline, thereby reducing the bulk of the myometrium. This process is repeated until the uterus can be removed or until a pseudocapsule of a fibroid can be grasped with a Leahy clamp or towel clip. Traction is then applied, and a "myomectomy" is performed.

When the intramyometrial coring technique is used, the myometrium above the site of the ligated vessels is incised parallel to the axis of the uterine cavity and serosa of the uterus. This incision is continued around the full circumference of the myometrium in a symmetric fashion beneath the uterine serosa. Traction is maintained on the cervix, and the avascular myometrium is cut to allow the undisturbed endometrial cavity, with a thick layer of myometrium, to be delivered with the cervix. As a result, the inside of the uterus with its unopened endometrial cavity is brought closer to the operator. Incision of the lateral portions of the myometrium medial to the remaining attachment of the broad ligament results in considerable additional descent of the uterus and greatly increases the mobility of the uterine fundus. The uterus is converted from a globular to an elongated tissue mass. The cored uterus is removed by clamping the utero-ovarian pedicle and fallo-pian tubes.

In a retrospective comparison of 383 patients undergoing abdominal hysterectomy or vaginal hysterectomy with uterine morcellation, length of stay and perioperative complications were significantly increased with abdominal hysterectomy. Therefore, it appears that vaginal hysterectomy with uterine

morcellation is safe and allows for an increased number of women to undergo vaginal hysterectomy.

McCall Culdoplasty

Although McCall culdoplasty has been thought by some surgeons to help decrease future enterocele formation (100), whether this is accurate remains open to debate.

An absorbable suture is placed through the full thickness of the posterior vaginal wall at the point of the highest portion of the vaginal vault. The patient's left uterosacral ligament pedicle is grasped and sutured. The suture then incorporates the posterior peritoneum,

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between the uterosacral ligaments and the right uterosacral ligament. The suture is completed by passing the needle from the inside to the outside at the same point at which it was begun. The suture is tied, thereby approximating the uterosacral ligaments and the posterior peritoneum.

Schuchardt Incision

When vaginal exposure is difficult, the Schuchardt incision may be used (100). If the surgeon is right-handed, the incision is made on the patient's left side. To decrease blood loss, the area can be infiltrated with lidocaine-containing epinephrine. The incision follows a curved line from the 4-o'clock position at the hymenal margin to a point halfway between the anus and the ischial tuberosity. The incision may be continued as high as necessary in the vaginal vault to gain exposure. The depth of the incision is the medial portion of the pubococcygeus muscle, which may be divided in extreme cases. The incision must be closed in layers at the completion of the procedure.

Intraoperative Complications

Bladder Injury

Injury to the urinary bladder is one of the most common intraoperative complications associated with hysterectomy. **If the bladder is inadvertently entered, repair generally should be performed when the injury is discovered and not delayed until completion of surgery (87).** When bladder injury is recognized, the edges of the wound should be mobilized to assess the full extent of the injury and to allow repair without tension. This assessment should include visualization of the trigone to exclude injury to that area. The bladder may then be repaired with a single- or double-layered closure with a small-caliber absorbable suture. *Methylene blue* or a dye of sterile milk formula can be instilled into the bladder to ensure that the repair is adequate.

Bowel Injury

Because patients with suspected pelvic adhesions or obvious pelvic disease are excluded as candidates for vaginal hysterectomy, bowel injuries do not occur often. Bowel injuries more often are associated with the performance of a posterior colporrhaphy and are usually confined to the rectum (87,100).

If the rectum is entered, the injury is repaired with a single- or double-layer closure using a small-caliber absorbable suture, followed by copious irrigation. Postoperatively, the patient should be given a stool softener and a low-residue diet.

Hemorrhage

Intraoperative hemorrhage invariably is the result of failure to ligate securely a significant blood vessel, bleeding from the vaginal cuff, slippage of a previously placed ligature, or avulsion of tissue before clamping (100). Most intraoperative bleeding can be avoided with adequate exposure and good surgical technique. Using square knots with attention to proper knot-tying mechanisms will prevent bleeding in most cases. Likewise, the use of Heaney-type sutures may minimize ligature slippage and subsequent bleeding from bulky pedicles. When bleeding does occur, blind clamping, which may endanger the ureter, should be avoided. The bleeding vessel should be identified and precisely ligated, with visualization of the ureter if necessary. **If the location of the ureter is in question, it should be visualized before suturing a bleeding vessel.** Although excessive blood loss occasionally occurs despite these precautions, it should be infrequent.

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Perioperative Care

Bladder Drainage

Postoperative bladder drainage should be employed after any procedure in which spontaneous, complete voiding is not anticipated. Reasons to consider closed bladder drainage include significant local pain, additional vaginal reparative procedures, surgery for stress incontinence, the use of a vaginal pack, and patient anxiety.

After vaginal hysterectomy without additional repair, most patients can void spontaneously, and therefore, catheter drainage is not required. The relative amount of pain after a vaginal hysterectomy is less than with abdominal hysterectomy and, in the absence of additional repairs or a pack, no obstructive effect should be present.

If the patient does not tolerate pain well postoperatively or is extremely anxious, the transurethral insertion of a 16-Fr. catheter after completing surgery is warranted. This catheter may also be inserted postoperatively if the patient is unable to void spontaneously on two attempts. Closed-catheter drainage after vaginal hysterectomy usually is not necessary for longer than 24 hours. The catheter is removed without clamping, and there is no need to obtain a urine specimen for culture and sensitivity.

Diet

Although little manipulation of the bowel occurs during vaginal hysterectomy, there is some slowing of gastrointestinal motility. This slowing rarely occurs to a degree that limits some form of oral intake soon after surgery. Most patients experience some degree of nausea after surgery, which, combined with drowsiness from analgesics, usually makes them disinterested in food on the evening after surgery. A clear liquid diet is suitable during the first night after surgery. On the first full postoperative day, a regular diet can usually be consumed. **The patient is often the best judge of what she can tolerate.**

Perioperative Complications of Hysterectomy

A comprehensive discussion of postoperative complications after gynecologic surgery is presented in Chapter 20.

Wound Infections

Wound infections occur after 4% to 6% of abdominal hysterectomies (29).

Measures believed to reduce the incidence of wound infections include a preoperative shower, no removal of hair, or if hair removal is necessary, removal of hair with clippers in the operating room, use of adhesive drapes and prophylactic antibiotics, and delayed primary closure (see Chapter 20).

Hemorrhage

Immediately after hysterectomy, hemorrhage may become apparent in one of two ways (91). **First, bleeding from the vagina may be noted by the nursing staff or physician within the first few hours after surgery. Second, and less commonly, the patient may be noted to have little bleeding from the vagina but deteriorating vital signs manifested by low blood pressure and rapid pulse, falling hematocrit level, and flank or abdominal pain. The first presentation usually is in the form of bleeding from the vaginal cuff or one of the pedicles. The second presentation may be a retroperitoneal hemorrhage.** Each situation is approached differently in its evaluation and treatment, but both involve the same general principles of rapid diagnosis, stabilization of vital signs, appropriate fluid and blood replacement, and constant surveillance of the patient's overall condition.

After vital signs are assessed, attention should be directed to the amount of bleeding. A small amount of bleeding is expected after any vaginal hysterectomy. However, **steady**

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bleeding 2 to 3 hours after surgery suggests lack of hemostasis. The patient should be taken promptly to the examining room, where the operative site is viewed using a large speculum and good lighting. If bleeding is not excessive, the vaginal cuff can be inspected, and in many instances, bleeding from the cuff edge will be found. Hemostasis can easily be achieved with one or two sutures placed through the mucosa.

If bleeding is excessive or appears to be coming from above the cuff, or if the patient is too uncomfortable to tolerate adequate examination, she should be taken to the operating room. General anesthesia should be administered and the vaginal operative site should be thoroughly explored. Any bleeding point may be sutured or ligated. However, bleeding that is coming from above the cuff or is extremely heavy usually cannot be controlled through the vaginal route. An exploratory laparotomy is necessary to examine the pelvic floor, identify and isolate the bleeding vessel, and achieve hemostasis. **The ovarian vessels and uterine arteries should be thoroughly inspected because they often are the source of excessive vaginal bleeding.** If it is difficult to localize bleeding to a specific pelvic vessel, or if these maneuvers do not work, ligation of the hypogastric artery may be performed.

In the patient with little vaginal bleeding in whom vital signs have deteriorated, retroperitoneal hemorrhage should be suspected. Input and output should be monitored. Hematocrit assessment, along with cross-matching, should be performed immediately. Examination may reveal tenderness and dullness in the flank. In cases of intraperitoneal bleeding, abdominal distention may occur. Diagnostic radiologic studies can be used to confirm the presence of retroperitoneal or intra-abdominal bleeding. Ultrasonography is one option for viewing low pelvic hematomas; CT provides better visualization of retroperitoneal spaces, however, and can delineate a hematoma.

If the patient's condition stabilizes rapidly with intravenous fluids, one of two approaches may be used for continued care. The first is to give the patient a transfusion and follow serial hematocrit assessments and vital signs. In many instances, retroperitoneal bleeding will tamponade and stop, forming a hematoma

that may eventually be resorbed. The risk with this approach is that the hematoma will later become infected, necessitating surgical drainage. In some instances when the patient's condition is stable, radiologic embolization may be considered.

Another option is to perform abdominal exploratory surgery while the patient's condition is stable. This approach adds the morbidity of a second procedure but avoids the possibility of the patient's condition deteriorating with continued delay or the formation of a pelvic abscess. Once adequate exposure is obtained, the peritoneum over the hematoma should be opened, and the blood should be evacuated. All bleeding vessels should be identified and ligated. Again, if bleeding is difficult to control, consideration should be given to unilateral or bilateral ligation of the anterior division of the internal iliac artery. Once hemostasis is achieved, the pelvis should be drained using a closed system.

Urinary Tract Complications

Urinary Retention

Urinary retention after hysterectomy is an uncommon occurrence (32). If the urethra is unobstructed and retention occurs, it is usually the result of either pain or bladder atony resulting from anesthesia. Both are temporary effects.

If a catheter was not placed after surgery, retention can be relieved initially with the insertion of a Foley catheter for 12 to 24 hours. Most patients are able to void after the catheter is removed 1 day later. If the patient still has trouble voiding and urethral spasm is suspected, success often can be achieved with a skeletal muscle relaxant such as

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diazepam (2 mg twice a day). In most cases, waiting is the best course, and voiding usually occurs spontaneously.

Ureteral Injury

In patients who develop flank pain soon after vaginal hysterectomy, ureteral obstruction should be suspected. The incidence of ureteral injury is lower with vaginal hysterectomy than with abdominal hysterectomy (86). One risk factor for its occurrence is total uterine prolapse, in which the ureters are drawn outside the bony pelvis.

In a patient with flank pain in whom ureteral obstruction is suspected, a CT urogram and a urinalysis should be performed (83). If obstruction is noted on CT scan, it is usually present near the ureterovesical junction. The first immediate step should be attempted passage of a catheter through the ureter under cystoscopic guidance. If a catheter can be passed through the ureter, it should be left in place for at least 4 to 6 weeks, allowing sutures to absorb and the obstruction or kinking to release. If the catheter cannot be passed through the ureter, the best course is to perform abdominal exploratory surgery and repair the ureter at the site of obstruction (82,83,84,85,86,87).

Vesicovaginal Fistula

Vesicovaginal fistulas occur most often after total abdominal hysterectomy for benign gynecologic disease (86). Intraoperative steps to avoid the formation of a vesicovaginal fistula include correct identification of the proper plane between the bladder and cervix, sharp rather than blunt dissection of the bladder, and care in clamping and suturing the vaginal cuff. The development of a postoperative vesicovaginal fistula after hysterectomy is

rare; the incidence is as low as 0.2% (85,86).

Patients who have a postoperative vesicovaginal fistula develop a watery vaginal discharge 10 to 14 days after surgery. Some fistulas resulting from surgery are noted as early as the first 48 to 72 hours after surgery (87). After vaginal examination with a speculum, the diagnosis can usually be confirmed with the insertion of a cotton tampon into the vagina followed by the instillation of *methylene blue* or *indigo carmine* dye through a transurethral catheter. If the tampon stains blue, a vesicovaginal fistula is present. If no staining occurs, however, the presence of a ureterovaginal fistula must be ruled out by the intravenous injection of 5 mL of *indigo carmine* dye. Within 20 minutes, the tampon should stain blue if a ureterovaginal fistula is present. A CT urogram should also be performed to rule out ureteral obstruction.

If a vesicovaginal fistula is diagnosed, a Foley catheter should be inserted for prolonged drainage. Up to 15% of fistulas close spontaneously with 4 to 6 weeks of continuous bladder drainage. If closure has not occurred by 6 weeks, operative correction is necessary. Waiting 3 to 4 months from the time of diagnosis before operative repair is recommended to allow reduction of inflammation and to improve vascular supply. After vaginal hysterectomy, the fistula site is above the bladder trigone and away from the ureters. Vaginal repair can be anticipated in most patients. The surgical correction generally is undertaken in a four-layered closure: the bladder mucosa, the seromuscular layer, the endopelvic fascia, and the vaginal epithelium.

Incidental cystotomy at the time of hysterectomy is more common than vesicovaginal fistula. When repaired correctly, cystotomy rarely results in the development of a fistula (85).

Prolapse of the Fallopian Tube

Posthysterectomy prolapse of the fallopian tube is a rare event and often is confused with granulation tissue at the vaginal apex (32). Predisposing factors for the development of

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fallopian tube prolapse include development of a hematoma and an abscess at the vaginal apex. Approximately one half of patients undergoing vaginal hysterectomy form some granulation tissue at the vaginal vault. **In patients in whom granulation tissue persists after attempts to cauterize it or pain is experienced with attempts to remove it, fallopian tube prolapse should be suspected.** A biopsy of the area is warranted and usually reveals tubal epithelium if a fallopian tube is present.

If fallopian tube prolapse is diagnosed, it should be repaired with surgery. In general, the surrounding vaginal mucosa should be opened and undermined widely. The tube is then ligated high and removed, followed by closure of the vaginal mucosa.

Discharge Instructions

Before discharging the patient, instructions should be reviewed. Printed postoperative instructions are helpful to the patient and should include the following information:

- Avoid strenuous activity for the first 2 weeks, and increase activity level gradually.
- Avoid heavy lifting, douching, or sexual intercourse until instructed by the physician.

Bathe as needed using shower or tub baths.

- Follow a regular diet.
- Avoid straining for a bowel movement or urination. For constipation, use *Milk of Magnesia* or *Metamucil* (1 tsp in juice).
- Call the physician if excessive vaginal bleeding or fever occurs.
- Schedule a return appointment at the time specified by the physician.

The physician should provide telephone numbers for emergencies both during and after office hours. Typically, the first postoperative visit is scheduled about 4 weeks after discharge from the hospital. At the time of that visit, the patient should be ambulating well, and vaginal discharge or bleeding should be minimal. Speculum examination of the cuff should be gentle and cursory, but the patient should be assured that the healing process is proceeding normally. Finally, the patient's questions should be answered, and advice should be given on increasing her activity level, including sexual activity, work, and normal household activity.

Psychosomatic Aspects

The decision to proceed with hysterectomy should be made jointly by the patient and her physician. Factors leading a patient or her physician to choose hysterectomy and reasons that patients with similar conditions choose different treatments are uncertain. For many patients, the decision to undergo hysterectomy may be sudden. They face the potential risks of anesthesia and surgery, and, if premenopausal, they must also cope with the loss of menstruation and the ability to procreate. Many women are concerned that the procedure will result in a loss of femininity, a decrease in sexual satisfaction, or an increase in interpersonal problems with their spouses. The concern over the loss of the reproductive tract is greater than that related to the loss of other intra-abdominal organs (102,103). To minimize the possibility that the patient has a poor outcome, preoperative counseling and preparation are essential.

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In a study of 23 women who had hysterectomy, most regretted the loss of menstruation, even those who had experienced dysmenorrhea (104). Several of these women viewed the menstrual cycle as a way for the body to "rid itself of waste," and they felt better after the menstrual phase of their cycle.

Depression

There is wide variation in women's responses to hysterectomy. Most studies suggest that there is little evidence that hysterectomy increases the risk of depression. Some investigators have reported depression and an increased incidence of psychiatric symptoms after hysterectomy (105,106). One study concluded that almost twice as many women were admitted to a psychiatric hospital after pelvic operations compared with other types of surgery (107). However, others have not found such an association (108), and some report a decrease in symptoms after hysterectomy (109,110,111,112,113). **The impact of hysterectomy on the development of depression is unknown because most studies are retrospective**

and not well controlled for preoperative depression (see Chapter 12).

Patients who had a moderate amount of preoperative anxiety do much better postoperatively than patients with little or no anxiety or patients who had an exaggerated response (114). Both long delays before surgery and a very short time before surgery increase patients' anxiety. Thus, women should be scheduled for surgery several weeks in advance to avoid this problem (114). Women who planned to have children in the future had more problems during the immediate postoperative period. The patient's response to previous loss (eg, death of family members) predicted her response after hysterectomy (115).

Sexuality

The incidence of sexual dysfunction after hysterectomy ranges from 10% to 40%. Estimates vary based on study variations, cultural variations, and the definitions used to determine the diagnosis. Some report a decrease in libido after hysterectomy, whereas others suggest that libido is increased because of the reduced fear of unwanted pregnancy (106,116). Humphries found that most patients do not experience a change in their sexual practices after hysterectomy (117), whereas others report a deterioration of sexual relations (118). Preoperative anxiety about sexual functioning often is associated with an overall deterioration of sexual relations (119).

Hysterectomy does not cause psychiatric sequelae or diminished sexual functioning in most patients. The best predictor of satisfaction after hysterectomy is the patient's preoperative understanding of the procedure. **The best predictor of postoperative sexual functioning is the patient's preoperative sexual satisfaction.** Preoperatively, these issues should be discussed with the patient, and her questions and concerns should be addressed to decrease the fear and anxiety associated with surgery.

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23

Lower Urinary Tract Disorders

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- **Bladder storage and emptying depend on a complex interplay between the brain, spinal cord, bladder, urethra, and pelvic floor.**
- **Urinary incontinence is common in women and is generally treated successfully with a range of nonsurgical and surgical treatments.**
- **Stress urinary incontinence occurs with increases in abdominal pressure (such as coughing, running, lifting) and can be treated with pelvic muscle exercises, vaginal devices, lifestyle changes, and surgery.**
- **Urge urinary incontinence occurs with a sudden sense of urgency (such as on the way to the bathroom or when washing hands) and can be treated with bladder training, medications, lifestyle changes, and neuromodulation.**
- **Bladder pain remains a challenging and poorly understood entity.**

Physiology of Micturition

The bladder is a complex organ that has a relatively simple function: to store urine effortlessly, painlessly, and without leakage and to discharge urine voluntarily, effortlessly, completely, and painlessly. To meet these demands, the bladder must have normal anatomic support as well as normal neurophysiologic function.

Normal Urethral Closure

Normal urethral closure is maintained by a combination of intrinsic and extrinsic factors. The *extrinsic* factors include the levator ani muscles, the endopelvic fascia, and their attachments to the pelvic sidewalls and the urethra. This structure forms a hammock beneath the urethra that responds to increases in intra-abdominal pressure by tensing, allowing the urethra to be closed against the posterior supporting

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shelf (Fig 23.1). When this supportive mechanism becomes faulty for some reason—the endopelvic fascia has detached from its normal points of fixation, muscular support has weakened, or a combination of these two processes—normal support is lost, and anatomic hypermobility of the urethra and bladder neck develops. For many women, this loss of support is severe enough to cause loss of closure during periods of increased intra-abdominal pressure, resulting in stress incontinence. However, many women remain continent in spite of loss of urethral support (1).

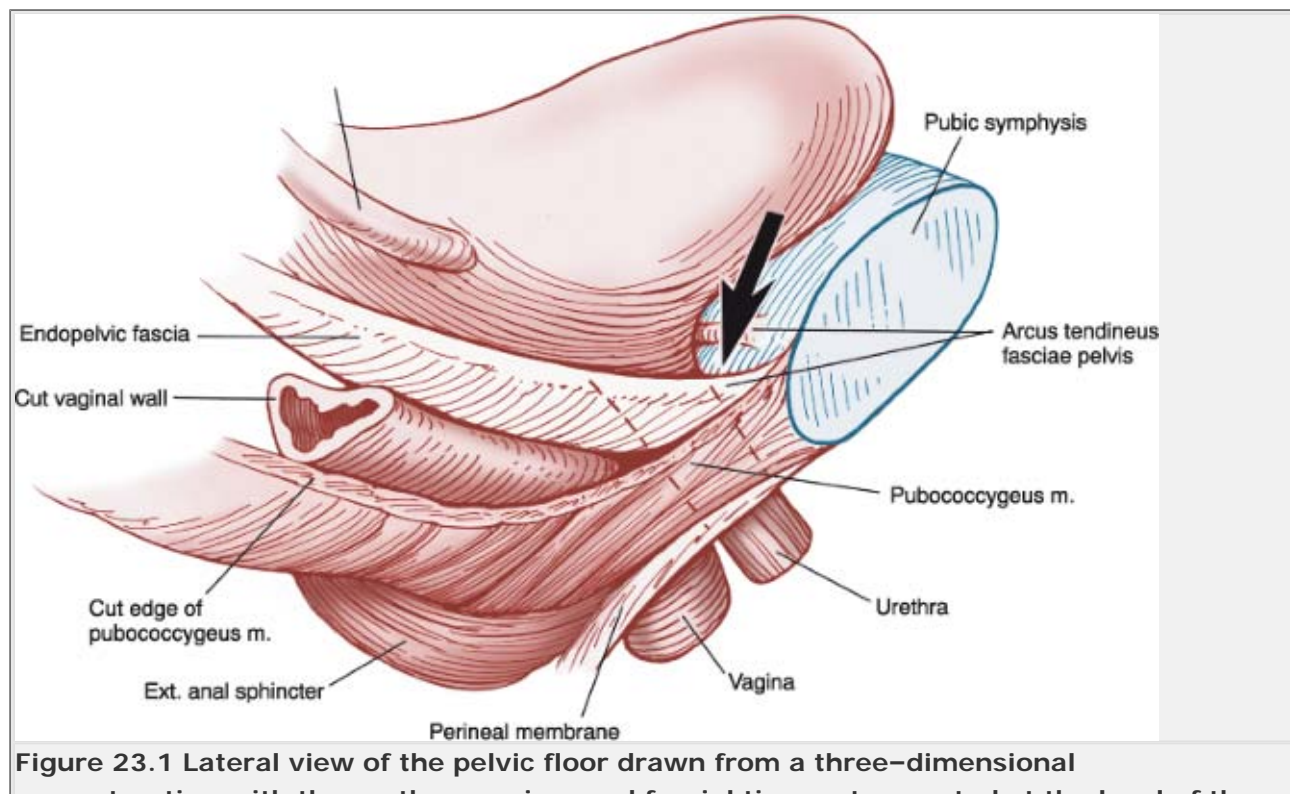


Figure 23.1 Lateral view of the pelvic floor drawn from a three-dimensional reconstruction with the urethra, vagina, and fascial tissues transected at the level of the vesical neck. Note how the urethra is compressed against the underlying supportive tissues by the downward force (arrow) generated by a cough or sneeze. (From Delancey J. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. *Am J Obstet Gynecol* 1994;170:1718, with permission.)

The *intrinsic* factors contributing to urethral closure include the striated muscle of the urethral wall, vascular congestion of the submucosal venous plexus, the smooth muscle of the urethral wall and associated blood vessels, the epithelial coaptation of the folds of the urethral lining, urethral elasticity, and the tone of the urethra as mediated by α -adrenergic receptors of the sympathetic nervous system.

Effective urethral closure is maintained by the interaction of extrinsic urethral support and intrinsic urethral integrity, each of which is influenced by several factors (muscle tone and strength, innervation, fascial integrity, urethral elasticity, coaptation of urothelial folds, urethral vascularity). In the clinical setting, damaged urethral support is manifested clinically by urethral hypermobility, which often results in incompetent urethral closure during physical activity and presents as stress urinary incontinence. Intrinsic urethral functioning is more complicated and is not nearly as well understood as incontinence related to loss of urethral support (2).

Clinical appreciation of the importance of extrinsic support and intrinsic urethral function led to the separation of stress incontinence into two broad types:

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- **Incontinence caused by anatomic hypermobility of the urethra**
- **Incontinence caused by intrinsic sphincteric weakness or deficiency**

Surgical approaches have been based on this arbitrary distinction, with pubovaginal sling recommended for women with intrinsic sphincter deficiency and a colposuspension (also known as retropubic urethropexy) for those with hypermobility. This rationale was based initially on a small study in which women younger than age 50 years with urethral closure pressure less than 20 cm H₂O had a higher failure rate after a Burch colposuspension than did women with a closure pressure greater than 20 cm H₂O (3). No difference in outcome was seen in women older than 50 years. More recently, this dichotomy has been called into question, based on the observation that all women with stress incontinence have some degree of sphincter weakness, regardless of whether they have hypermobility. Currently, it is not known whether women with more severe sphincter weakness have improved success with a specific type of surgery or whether they are more likely to experience treatment failure with any surgery.

The Bladder

The bladder is a bag of smooth muscle that stores urine and contracts to expel urine under voluntary control. It is a low-pressure system that expands to accommodate increasing volumes of urine without an appreciable rise in pressure. This function appears to be mediated primarily by the sympathetic nervous system.

During bladder filling, there is an accompanying increase in outlet resistance. The bladder muscle (the detrusor) should remain inactive during bladder filling, without involuntary contractions. When the bladder has filled to a certain volume, fullness is registered by tension-stretch receptors, which signal the brain to initiate a micturition reflex. This reflex is permitted or not permitted by cortical control mechanisms, depending on the social circumstances and the state of the patient's nervous system. Normal voiding is accomplished by voluntary relaxation of the pelvic floor and urethra, accompanied by sustained contraction of the detrusor muscle, leading to complete bladder emptying.

Innervation

The lower urinary tract receives its innervation from three sources: (i) the sympathetic and (ii) parasympathetic divisions of the autonomic nervous system, and (iii) the neurons of the somatic nervous system (external urethral sphincter).

The *autonomic nervous system* consists of all efferent pathways with ganglionic synapses that lie outside the central nervous system. The sympathetic system primarily controls bladder storage, and the parasympathetic nervous system controls bladder emptying. The somatic nervous system plays only a peripheral role in neurologic control of the lower urinary tract through its innervation of the pelvic floor and external urethral sphincter.

The sympathetic nervous system originates in the thoracolumbar spinal cord, principally T11 through L2 or L3 (see Chapter 6). The ganglia of the sympathetic nervous system are located close to the spinal cord and use acetylcholine as the preganglionic neurotransmitter. The postganglionic neurotransmitter in the sympathetic nervous system is norepinephrine, and it acts on **two types of receptors: α receptors, located principally in the urethra and bladder neck, and β receptors, located principally in the bladder body. Stimulation of α receptors increases urethral tone and thus promotes closure, whereas α -adrenergic receptor blockers have the opposite effect. Stimulation of β receptors decreases tone in the bladder body.**

The parasympathetic nervous system controls bladder motor function—bladder contraction and bladder emptying. The parasympathetic nervous system originates in the sacral spinal cord, primarily in S2 to S4, as does the somatic innervation of the pelvic

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floor, urethra, and external anal sphincter. Sensation in the perineum is also controlled by sensory fibers that connect with the spinal cord at this level. For this reason, examination of perineal sensation, pelvic muscle reflexes, and pelvic muscle or anal sphincter tone is relevant to clinical evaluation of the lower urinary tract. The parasympathetic neurons have long preganglionic neurons and short postganglionic neurons, which are located in the end organ. Both the preganglionic and postganglionic synapses use acetylcholine as their neurotransmitter, acting on muscarinic receptors. **Because acetylcholine is the main neurotransmitter used in bladder muscle contraction, virtually all drugs used to control detrusor muscle overactivity have anticholinergic properties.**

Bladder storage and bladder emptying involve the interplay of the sympathetic and parasympathetic nervous systems. The modulation of these activities appears to be influenced by a variety of nonadrenergic, noncholinergic neurotransmitters and neuropeptides, which fine-tune the system at various facilitative and inhibitory levels in the spinal cord and higher areas of the central nervous system (4,5,6). Thus, neuropathology at almost any level of the neurourogenic axis can have an adverse effect on lower urinary tract function.

Micturition

Micturition is triggered by the peripheral nervous system under the control of the central nervous system. It is useful to consider this event as occurring at a micturition threshold, a bladder volume at which reflex detrusor contractions occur. The threshold volume is not fixed; rather, it is variable and can be altered depending on the contributions made by sensory afferents from the perineum, bladder, colon, and rectum as well as input from the higher centers of the nervous system. The micturition threshold is, therefore, a floating threshold that can be altered or reset by various influences.

The spinal cord and higher centers of the nervous system have complex patterns

of inhibition and facilitation. The most important facilitative center above the spinal cord is the pontine–mesencephalic gray matter of the brain stem, often called the *pontine micturition center*, which serves as the final common pathway for all bladder motor neurons. Transection of the tracts below this level leads to disturbed bladder emptying, whereas destruction of tracts above this level leads to detrusor overactivity. The cerebellum serves as a major center for coordinating pelvic floor relaxation and the rate, force, and range of detrusor contractions, and there are multiple interconnections between the cerebellum and the brain–stem reflex centers. Above this level, the cerebral cortex and related structures exert inhibitory influences on the micturition reflex. Thus, the upper cortex exerts facilitative influences that release inhibition, permitting the anterior pontine micturition center to send efferent impulses down the complex pathways of the spinal cord, where a reflex contraction in the sacral micturition center generates a detrusor contraction that causes bladder emptying.

A normal lower urinary tract is one in which the bladder and urethra store urine without pain until a socially acceptable time and place arises, at which point voiding occurs in a coordinated and complete fashion. Lower urinary tract disorders include disorders of storage (such as urinary incontinence), emptying (such as urinary hesitancy and retention), and sensation (such as urgency or pain).

Current definitions for these disorders are depicted in Table 23.1.

Urinary Incontinence

Definitions

Defining urinary incontinence would seem an easy task: women that leak urine must be “incontinent.” **The International Continence Society, an organization charged with defining the various disorders of pelvic floor dysfunction, recently defined incontinence**

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as “the complaint of any involuntary leakage of urine” (7). Unfortunately, this definition does not take into account the wide variation in this symptom and the disruption it causes. For example, half of young nulliparous women report occasional minor urine leakage; for most this is not neither a bother nor a symptom for which they would seek treatment. At the other extreme, 5% to 10% of adult women have severe leakage daily. These women often dramatically alter their lives because of leakage, curtailing activities, social outings, and intimacy. Many suffer marked deterioration in self–esteem. In between these two extremes lies another one–third of adult women who report leakage at least weekly, but without the same degree of life–altering severity as the women previously noted.

Table 23.1 Classification and Definition of Lower Urinary Symptoms in Women

I. Abnormal Storage	
<i>Incontinence (symptom)</i>	The complaint of any involuntary leakage of urine
<i>Stress urinary incontinence (symptom)</i>	The complaint of involuntary leakage on effort or exertion, or on sneezing or coughing
<i>Stress urinary incontinence (sign)</i>	Observation of involuntary leakage from the urethra, synchronous with exertion/effort, or sneezing or coughing
<i>Urge urinary incontinence (symptom)</i>	The complaint of involuntary leakage accompanied by or immediately preceded by urgency
<i>Mixed incontinence</i>	Complaints of both stress and urge incontinence
<i>Continuous urinary incontinence</i>	Complaint of continuous leakage.

Frequency The number of voids per day, from waking in the morning until falling asleep at night

Increased daytime frequency Complaint by the patient that she voids too often

Nocturia Complaint that the individual has to wake at night one or more time to void (each void is preceded and followed by sleep)

Nocturnal enuresis Complaint of loss of urine during sleep

Extraurethral incontinence The observation of urine leakage through channels other than the urethra

Uncategorized incontinence The observation of involuntary leakage that cannot be classified into one of the above categories based on signs and symptoms

Overactive bladder syndrome (OAB), urge syndrome, urgency–frequency syndrome Can all be used to describe urgency, with or without urge incontinence, usually with frequency and nocturia

II. Abnormal Emptying

Hesitancy Trouble initiating voiding

Straining to void Voiding accompanied by abdominal straining

Poor stream Decreased force of flow of the urinary stream

Intermittent stream A stop–and–start pattern of urination

Incomplete emptying A persistent feeling of bladder fullness after voiding

Postmicturition dribble Urine loss occurring just after normal voiding has been completed

Acute urinary retention Sudden inability to void, resulting in painful bladder overdistention and the need for catheterization to obtain relief

Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21:167–178.

Collectively, these women assume a substantial cost burden. The total annual cost to care for patients with incontinence in the United States is estimated at \$11.2 billion in the community and \$5.2 billion in nursing homes (8). In the United States, much of this cost is borne directly by women in the form of incontinence pads and excess laundry costs. Despite the burden imposed by leakage, many women do not discuss this symptom with a

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health care professional. For some women, this is because the leakage does not bother them, whereas others are embarrassed and suffer in silence. Still others do not raise this issue because they mistakenly believe the only treatment option is surgical. Thus, it is incumbent on the provider to ask women about leakage.

Studies have shown that there is little relationship between the volume of urine lost and the distress that it causes a patient (9). The degree to which women are bothered by leakage is influenced by various factors, including cultural values and expectations regarding urinary continence and incontinence. **If the leakage is distressing to the patient, evaluation and treatment should be offered. Incontinence can almost always be improved and frequently can be cured, often using relatively simple, nonsurgical interventions.**

Types of Disorders

Stress Urinary Incontinence

Stress urinary incontinence occurs during periods of increased intra-abdominal pressure (e.g., sneezing, coughing, or exercise) when the intravesical pressure rises higher than the pressure that the urethral closure mechanism can withstand.

Stress urinary incontinence is the most common form of urinary incontinence in women and is particularly common in younger women. Active women are more likely to notice symptoms of stress urinary incontinence. In a survey of 144 collegiate female varsity athletes, 27% reported stress incontinence while participating in their sport (10). The activities most likely to produce urinary loss were jumping, high-impact landings, and running.

Stress incontinence is an interesting "disease" as the same symptoms have varying effects on different women. This condition is best thought of by a biobehavioral model that examines the interaction of three variables: (i) the biologic strength of the urethral sphincteric mechanism, (ii) the level of physical stress placed on the closure mechanism, and (iii) the woman's expectations about urinary control. This model explains the enormous variation that exists among the symptoms, the degree of demonstrable leakage, and a patient's response to her stress incontinence. Modification of any one of these factors may influence the patient's clinical status; for example, many patients give up certain physical activities (e.g., running, dancing, aerobics) when they experience stress incontinence. Limiting their activities may eliminate the incontinence problem, but it does so at a certain cost to their quality of life. Other women learn to cope with stress incontinence by adopting new body postures during physical activities that prevent them from leaking or by strengthening their pelvic muscles to compensate for increased exertion. Other women may be profoundly relieved to find out that the small amount of leakage they experience from time to time is not abnormal. In any case, the interaction of these three biopsychosocial factors opens up a variety of strategies for the management of stress incontinence. Surgical intervention is only one strategy, and it addresses only the biologic competence of the sphincteric mechanism rather than either of the other factors that interact to produce the clinical problem.

Urge Urinary Incontinence and Overactive Bladder

Although stress incontinence is the most common type of urinary continence in women, urge incontinence is the most common form of incontinence in older women (11). Urge urinary incontinence is the involuntary leakage of urine accompanied by or immediately preceded by urgency. This is a symptom-based diagnosis and may or may not be caused by detrusor overactivity, which is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase.

Women may also have related problems such as urgency, nocturia, and increased daytime frequency. The definition of nocturia is quantifiable: The woman wakes one or more times a night to void (7). The other symptoms are more subjective. Increased

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daytime frequency occurs when the patient considers that she voids too often. (Note that the term *pollakisuria* is used to describe this condition in many countries.)

Urgency is the sudden compelling desire to pass urine that is difficult to defer. Most women have experienced these symptoms during times of voluntary delays in voiding or increased fluid intake. However, urinary urgency implies more than just the feeling that all normal women have if they voluntarily delay voiding beyond a reasonable time (12). When a woman presents for treatment, she generally reports an intrusive, bothersome, persistent need to urinate that takes her attention away from other activities. Increased daytime frequency is often brought up as an issue when a woman experiences a change in her own voiding pattern.

There is very little information about what is "normal" in terms of voiding frequency.

Overactive bladder (OAB) is frequently defined in studies of pharmacologic agents as more than eight voids per 24 hours, a definition that was based on the 95th percentile of voids in a small sample of Scandinavian women (13). **More recent data from a broader sample of women in the United States suggests that the median number of voids per day is eight, and 95% of so-called normal women void 12 or fewer times per day (14).**

Detrusor overactivity is qualified, when possible, by cause and is termed *neurogenic detrusor overactivity* (formerly called *detrusor hyperreflexia*) when a neurological condition may account for the finding, and *idiopathic detrusor overactivity* (formerly called *detrusor instability*) when there is no defined cause.

The term *overactive bladder syndrome* also describes women with symptoms of urgency, frequency, and urge incontinence. It is referred to as *OAB-dry* when women with these symptoms do not leak urine, and *OAB-wet* when it is accompany by incontinence. It is important to note that a woman with severe urgency and a sense of impending leakage who remains dry may have the exact same bladder pathology as one with severe urgency and concomitant leakage. A woman with a strong urethral sphincteric mechanism may be able to avoid leakage during uninhibited bladder contractions, whereas one with a strong sphincter may remain dry but be disturbed by the urgency and impending sense of leakage.

Mixed Incontinence

As implied by the name, women with mixed incontinence have symptoms of both stress and urge urinary incontinence. Younger women are more likely to have stress incontinence alone, whereas in older women mixed and urge incontinence predominate. In a review of 15 population-based studies of women of all ages with urinary incontinence, a median of 49% (range 24%–75%) had stress urinary incontinence, 21% (range 7%–49%) had urge urinary incontinence, and 29% (range 11%–61%) had mixed urinary incontinence (15).

Functional and Transient Incontinence

Functional incontinence is more common in elderly women and refers to incontinence that occurs because of factors unrelated to the physiologic voiding mechanism. A woman who can't get to the bathroom quickly may often become incontinent.

Functional incontinence can be related to such factors as decreased mobility, musculoskeletal pain, or poor vision. Factors leading to transient urinary incontinence are, as the name implies, medically reversible conditions. **A useful mnemonic to help remember these factors is DIAPPERS (16,17) (Table 23.2).** These factors argue strongly for the inclusion of a thorough medical evaluation as part of the workup of any patient with urinary incontinence.

Extraurethral Incontinence

While most urinary incontinence represents unwanted urine loss through the urethra (transurethral incontinence), urine loss can also occur through abnormal openings. These

openings can be created by congenital causes or some form of trauma. The congenital causes of urinary incontinence are not common and usually are easy to diagnose. The most extreme cases are caused by **bladder exstrophy**, in which there is a congenital absence of the lower anterior abdominal wall and anterior portion of the bladder, resulting in the entire bladder opening directly to the outside (18). Such cases are diagnosed at birth. Before the advent

of modern reconstructive surgery, these infants usually died very early in life from sepsis.

Table 23.2 Reversible Causes of Incontinence

D	Delirium
I	Infection
A	Atrophic urethritis and vaginitis
P	Pharmacologic causes
P	Psychological causes
E	Excessive urine production
R	Restricted mobility
S	Stool impaction

Resnick NM, Yalla SV. Management of urinary incontinence in the elderly. *N Engl J Med* 1985; 313:800–805.

Ectopic ureter, a subtle congenital anomaly causing extraurethral urine loss, generally is detected early in life, but occasionally one may escape detection until adolescence or early adulthood (19). In infancy, an ectopic ureter should be suspected when a mother seeks care for her baby, whom she says is never dry. Normally, infants have periods of dryness interspersed with periods of wetness. Most commonly, the ectopic ureter drains into the vagina, but occasionally, it may drain into the urethra distal to the point of continence. This condition can be diagnosed by excretory urography.

A traumatic opening between the urinary tract and the outside is called a fistula. Vesicovaginal fistulas, located between the bladder and urethra, are most common, but fistulas may also occur between the vagina, uterus, or bowel, and the urethra, ureter, or bladder.

Worldwide, the most common cause of vesicovaginal fistulas is obstructed labor. This also was true in the Western world 150 years ago, but advances in the provision of basic obstetric services and advanced obstetric intervention have virtually eliminated this problem in developed countries. The rest of the world is not so fortunate.

Obstructed labor often occurs in rural areas where girls are married young (sometimes as early as 9 to 10 years of age) and where transportation is poor and access to medical services is limited. In such circumstances, pregnancy often occurs shortly after menstruation begins and before maternal skeletal growth is complete. When labor begins, cephalopelvic disproportion is common, and little can be done to correct fetal malpresentations. Women may be in labor as long as 5 to 6 days without intervention, and if they survive, they usually give birth to a stillborn infant. In such cases, the soft tissues of the pelvis have been crushed by constant pressure from the fetal head, leading to an ischemic vascular injury and subsequent tissue necrosis. When this tissue sloughs, a genitourinary or rectovaginal fistula develops. Many of these patients have complex or multiple fistulas, involving total destruction of the urethra and sloughing of the entire bladder base (Fig 23.2). Obstetric fistulas are frequently as large as 5 to 6 cm in diameter.

After such fistulas develop, the lives of these young women (most of whom are younger than 20 years of age) are ruined unless they can gain access to curative surgical services.

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The constant, uncontrolled dribble of urine makes them offensive to their husbands and family members. They can no longer live with their families. Most of them eventually become destitute social outcasts—and yet these are otherwise healthy functional young women.

The social and economic costs of this problem are enormous, yet it largely has been neglected by the world medical community. The morbidity associated with obstetric fistulas remains, along with the related maternal mortality, one of the single most neglected issues in international women's health care (20).

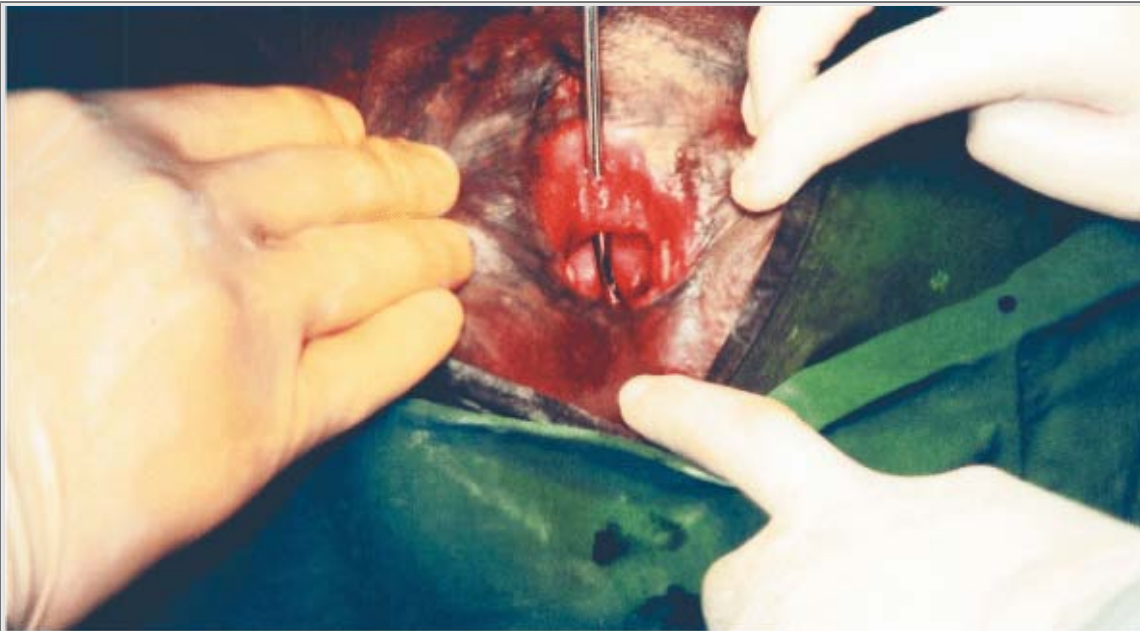


Figure 23.2 Moderate-sized obstetric vesicovaginal fistula. A metal probe has been placed through the urethra and is clearly visible through the bladder base. Copyright Worldwide Fistula Fund, used by permission.



Figure 23.3 Posthysterectomy fistulas. Note three small fistulas in a row.

In the industrialized world, **the most common causes of genitourinary fistulas are surgery, malignancy, and radiation therapy, alone or in combination. Most often, a vesicovaginal fistula develops after an otherwise uncomplicated vaginal or abdominal hysterectomy in which a small portion of the bladder was inadvertently trapped in a surgical clamp or was transfixated by a suture.** These fistulas most often occur at the vaginal apex and are no larger than 1 to 2 mm. The amount of urine that can leak through a fistula of any size, however, is enormous. Figure 23.3 shows a cystoscopic view of three small vesicovaginal fistulae, lined up where the cuff suture line would have been.

Although rare, vesicouterine fistulas are increasing in incidence as the rate of cesarean deliveries increases. Such fistulas are almost always associated with repeat cesarean deliveries. **The classic triad of vaginal urinary leakage, cyclic hematuria, and amenorrhea is known as Yousef's syndrome (21).**

Nocturia

Nocturia is the number of voids recorded during a night's sleep; each void is preceded and followed by sleep. To sort out whether nocturia is due to heightened urine production at night, the nocturnal urinary volume can be assessed from a bladder chart. Nocturnal urinary volume is defined as the total volume of urine passed between the time the woman goes to bed with the intention of sleeping and the time of waking with the intention of rising. Thus, it excludes the last void before going to bed but includes the first void after rising in the morning. Nocturnal polyuria is present when an increased proportion of the 24-hour output occurs at night.

Risk Factors for Urinary Incontinence

Most of the data about risk factors for urinary incontinence come from clinical trials or cross-sectional studies using survey design. Some risk factors have been more rigorously studied than others. Thus, the information available is limited in its general applicability and one cannot infer causality from it. Despite these limitations, **there is some evidence that age, pregnancy, childbirth, obesity, functional impairment, and cognitive impairment are associated with increased rates of incontinence or incontinence severity (15,22).** Some factors pertain more to certain age groups than others. For example, in studies of older women, childbirth no longer increases the risk of incontinence, possibly because of the presence of comorbidities and other factors that promote incontinence. Medical diagnoses that generally have been associated with urinary incontinence include diabetes, strokes, and spinal cord injuries. Other factors about which less is known or findings are contradictory include hysterectomy, constipation, occupational stressors, smoking, and genetics.

Pregnancy and delivery predispose women to stress urinary incontinence, at least during their younger years. Of women who have not borne children, those who are pregnant leak more often than their nonpregnant counterparts; about half of women report symptoms of stress urinary incontinence during pregnancy, but in most, the symptom resolves after delivery. In a prospective study, 32% of 305 primiparas developed stress urinary incontinence during pregnancy and 7% after delivery. By 1 year, only 3% reported stress urinary incontinence (23). However, 5 years later, 19% of women with no symptoms after the first delivery had stress urinary incontinence. Of women reporting stress urinary incontinence 3 months postpartum (in most of whom it had resolved by 1 year), 92% had such leakage 5 years later. Thus, transient postpartum leakage may be a marker for future incontinence.

Various changes happen after delivery that may predispose women to stress

urinary incontinence. Levator ani muscle strength decreases (24). About 20% of women develop a visible defect in the levator ani muscles after vaginal delivery (25). The bladder neck descends (26), and the pelvic muscles undergo partial denervation with

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pubdental neuropathy (27). In most studies, parity is strongly associated with urinary incontinence in younger women (28). However, in studies of women 60 years and older, parity is generally no longer an independent risk factor for incontinence (29). The reason for this is not well elucidated, but it may be because the changes in muscle, nerve, connective tissue, and hormonal function that occur with aging make other women "catch up" to those that developed incontinence at a younger age because of delivery trauma. Alternately, it may be that medical problems more common in older women account for a larger proportion of incontinence risk as women age.

Obesity deserves special mention for its role in causing or exacerbating stress incontinence. Many researchers have reported an association (that remains after adjusting for age and parity) between increased weight and body mass index (BMI), and urinary incontinence. For example, a dose-response relationship between BMI and severe urinary incontinence has been described (30). Compared with women with a BMI less than 25 kg/m², odds ratios (OR) for the following BMI groups were: 25-29, OR 2.0 (1.7-2.3); 30-34, OR 3.1 (2.6-3.7); 35-39, OR 4.2 (3.3-5.3); 40+, 5.0 (3.4-7.3).

Initial Evaluation

The initial evaluation of patients with incontinence requires a systematic approach to consider possible causes. The basic evaluation should include the following items: history (including assessment of quality of life and degree of bother from symptoms), physical examination, and simple primary care level tests. Most women can begin nonsurgical treatment after this basic evaluation.

History

A thorough medical history should be obtained from every incontinent patient. The history should include a review of symptoms, general medical history, review of past surgery, and current medications. The woman's most troubling symptoms must be ascertained—how often she leaks urine, how much urine she leaks, what provokes urine loss, what improves or worsens the problem, and what treatment (if any) she has had in the past. It is essential to keep the patient's chief symptom at the forefront to avoid inappropriate management. Consider, for example, a woman whose chief concern is that once a month, while leading a business seminar, she has a sudden, overwhelming urge to void following by precipitant emptying of her entire bladder content. She finds this leakage devastating, and is considering quitting her job because of her acute embarrassment. On occasion, she also leaks a few drops of urine during exercise, but this minor leakage does not bother her. During the evaluation, urodynamics reveal minimal stress urinary incontinence at capacity during strong coughing. No detrusor overactivity is seen. The patient is offered, and undergoes, a surgical procedure for her documented urodynamic stress incontinence. Not surprisingly, her chief symptom is not improved and she is devastated.

The general medical history may reveal systemic illnesses that have a direct bearing on urinary incontinence, such as diabetes mellitus (which produces osmotic diuresis if glucose control is poor), vascular insufficiency (which can lead to incontinence at night when peripheral edema is mobilized into the vascular system, resulting in increased diuresis), chronic pulmonary disease (which can lead to stress incontinence from chronic coughing), or a wide variety of neurologic conditions that

can affect the neurourologic axis at any point from the cerebral cortex to the peripheral nervous system. Medications that may affect the lower urinary tract are summarized in Table 23.3 (31,32,33,34).

Quality-of-life Measures

Physicians caring for incontinent women should ask them about how the incontinence specifically affects their lives and to what degree the incontinence bothers them. There often is discord between the objective symptom severity and subjective bother. Only by understanding each woman's situation can treatment be appropriately

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planned and response evaluated. Some women may be completely satisfied if they are able to sit through a movie without running to the bathroom, even if they leak urine at other times. Others may be satisfied only if they are 100% dry. Given that the latter is likely an unrealistic goal, knowing that the patient feels this way gives the provider the opportunity to educate her about the likely outcome of treatment.

Table 23.3 Medications that May Affect the Urinary Tract

1.	Sedatives such as the benzodiazepines may cause confusion and secondary incontinence, particularly for elderly patients.
2.	Alcohol may have similar effects to benzodiazepines and also impairs mobility and causes diuresis.
3.	Anticholinergic drugs may impair detrusor contractility and may lead to voiding difficulty and overflow incontinence. Drugs with anticholinergic properties are widespread and include antihistamines, antidepressants, antipsychotics, opiates, antispasmodics, and drugs used to treat Parkinson's disease.
4.	α -Agonists, which are often found in over-the-counter cold remedies, increase outlet resistance and may lead to voiding difficulty.
5.	α -Blockers, sometimes used to treat hypertension (e.g., prazosin, terazosin), may decrease urethral closure pressure and lead to stress incontinence.
6.	Calcium-channel blockers may reduce bladder smooth muscle contractility and lead to voiding problems or incontinence; they may also cause peripheral edema, which may lead to nocturia or nighttime urine loss.
7.	Angiotensin-converting enzyme inhibitors may result in a chronic and bothersome cough that can result in increasing stress urinary incontinence in an otherwise asymptomatic patient.

Physicians who have a large number of incontinence patients or who wish to evaluate patients in a more standardized fashion before and after treatment may choose to use one of several well-designed, validated quality-of-life measures available. An expert summary of the literature in this area conducted for the International Consultation on Incontinence recommended the instruments summarized in Table 23.4. These instruments were found to be valid, reliable, and responsive to change following standard psychometric testing.

Physical Examination

The physical examination of the patient with incontinence should focus on both general medical conditions that may affect the lower urinary tract as well as problems related to urinary incontinence. Such conditions include cardiovascular insufficiency, pulmonary disease, occult neurologic processes (e.g., multiple sclerosis, stroke, Parkinson's disease, and anomalies

of the spine and lower back), abdominal masses, and mobility. Key factors to assess during the physical examination are summarized in Table 23.5. **A Q-tip test has poor predictive value for determining either stress urinary incontinence diagnosis or predicting treatment success** (35). It is used by some clinicians to determine movement of the anterior vaginal wall with Valsalva. A woman with a fixed nonmobile urethra is a poor candidate for a surgery (such as a Burch colposuspension) designed to elevate the urethra. It is not possible to support an already well-supported urethra.

Table 23.4 Questionnaires to Assess Urinary Incontinence

The following questionnaires have been recommended by the International Consultation on Incontinence to assess symptoms of incontinence and impact of incontinence on quality of life in women.^a

Symptoms

Urogenital Distress Inventory. Shumaker SA, Wyman JF, Uebersax JS, et al.

Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. *Qual Life Res* 1994;3:291-306.

Urogenital Distress Inventory (UDI)-6 (short form). Uebersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. *Neurourol Urodyn* 1995;14:131-139.

Urge-UDI. Lubeck DP, Prebil LA, Peebles P, et al. A health related quality of life measure for use in patient with urge urinary incontinence: a validation study. *Qual Life Res* 1999;1999:337-344.

King's Health Questionnaire. Kelleher CJ, Cardozo LD, Khullar V, et al. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol* 1997;104:1374-1379.

Incontinence Severity Index. Sandvik H, Hunskaar S, Seim A, et al. Validation of a severity index in female urinary incontinence and its implementation in an epidemiological survey. *J Epidemiol Community Health* 1993;47:497-499

Quality of Life

Quality of life in persons with urinary incontinence (I-QOL). Wagner TH, Patrick DL, Bavendam TG, et al. Quality of life of persons with urinary incontinence: development of a new measure. *Urology* 1996;47:67-72.

Incontinence Impact Questionnaire. Wyman JF, Harkins SW, Taylor JR, et al. Psychosocial impact of urinary incontinence in women. *Obstet Gynecol* 1987;70:378-381.

Incontinence Impact Questionnaire (IIQ)-7 (short form). Uebersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women. The incontinence impact questionnaire and the urogenital distress inventory. *Neurourol Urodyn* 1995;14:131-139.

Urge-IIQ. Lubeck DP, Prebil LA, Peebles P, et al. A health related quality of life measure for use in patient with urge urinary incontinence: a validation study. *Qual Life Res* 1999;1999:337-344.

^a**Donovan JL, Badia X, Corcos J, et al.** Symptom and quality of life assessment. In: **Abrams P, Cardozo L, Khoury J, et al.**, eds. *Incontinence*. Plymouth, UK: Plymbridge Distributors Ltd, 2002.

Simple (Primary Care Level) Tests

It is important to realize that formal urodynamics tests are neither the only, nor the most important, tests of bladder function. Other simple tests that can easily be performed in the primary care setting provide useful information to guide patient care.

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Voiding Diary

A frequency/volume bladder chart (often termed a "bladder diary") is an invaluable aid in the evaluation of patients with urinary incontinence. A frequency/volume chart is a voiding record kept by the patient for several days. Patients are instructed to write down the time of every void on the chart and measure the amount of urine voided. The time of any incontinent episodes, as well as the specific activities associated with urine loss, should be recorded. If desired, the patient can also be instructed to keep a record of fluid intake. Although the type of intake may guide management suggestions, in most cases volume of intake can be estimated with some accuracy from the amount of urine produced.

A frequency/volume bladder chart provides vital information about bladder function that is not provided by formal urodynamics studies: 24-hour urinary output, the total number of daily voids, number of nighttime voids, the average voided volume, and

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the functional bladder capacity (largest volume voided in normal daily life). This information allows the clinician to confirm reports of urinary frequency with objective data and to determine whether part of the patient's problem is an abnormally high (or low) urinary output. The chart can also be used to calculate the volume of urine generated in nighttime hours versus daytime hours. Nighttime volume is calculated by adding output from voids that occur after the woman has fallen asleep for the night as well as the first morning void on awakening for the day. Older women sometimes have a marked shift in urine production, with more than half of their urine output generated during sleeping hours (Fig. 23.4). Demonstrating this on the voiding diary may lead to further treatment options.

Table 23.5 Physical Examination of a Woman with Lower Urinary Tract Dysfunction

Neurologic
Mental status
Perineal sensation
Perineal reflexes
Patellar reflexes
Abdominal examination
Masses
Cardiovascular
Congestive heart failure
Lower extremity edema
Mobility
Gait assessment
Pelvic examination
Prolapse
Atrophy
Levator muscle palpation (symmetry, ability to squeeze)
Anal sphincter function
Test of urethral mobility (e.g., Q-tip test)

Urinalysis

Examination of the urine by dipstick testing and microscopy is done to exclude infection, hematuria, and metabolic abnormalities. **Hematuria cannot be diagnosed on the results of a dipstick test alone; confirmation by microscopic evaluation is mandatory.**

If a urinary tract infection is documented by microscopy or culture, it is reasonable to see whether urinary tract symptoms improved with eradication of bacteriuria. Occasionally, a simple urinary tract infection causes the onset or exacerbation of urinary incontinence. However, **some women, particularly older ones, have asymptomatic bacteriuria that truly is asymptomatic; thus, if attempted treatment of a woman with bacteriuria but without classic urinary tract infection symptoms (such as dysuria, urgency, frequency) does not improve incontinence, further antibacterial treatment is generally unnecessary.**

If hematuria as well as bacteriuria is found, the urine should be rechecked after eradication of the bacteriuria. **Hematuria found in the absence of bacteriuria may need further evaluation to rule out kidney or bladder tumors;** the necessity for and extent of the evaluation depends on concomitant risk factors and the clinical presentation. If

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malignancy is suspected, bladder biopsy should be performed by the surgeon who would treat the patient in the event a malignancy is discovered.

Number of pads changed today 1
 Type of pad used Maxi pad

	Urinate in toilet (time and amount)	Accident (time)	Activity during accident	Fluid intake (time, type, amount)
To Bed	2200 240 cc			1 glass water
	0300 660 cc	0300	Leak on way to bathroom	
	0500 540 cc	0500	Preparing to urinate	
Up For Day	0700 150 cc			16 oz coffee 1 cup water
	0845 35 cc			
	1145 160 cc			
	1200			16 oz lemonade
	1540 60 cc			
	1800 100 cc			2 glasses wine 2 cups water
	1940 60 cc			16 oz diet coke 1 glass water

Figure 23.4 Voiding diary (also called bladder chart). Daytime frequency is seven. The patient has nocturia (gets up to void two times during sleeping hours) and also has nocturnal polyuria (an increased proportion of the 24-hour output occurs at night; note that nighttime urine output excludes the last void before sleep but includes the first void of the morning). She has urge incontinence, likely caused by the relatively larger bladder volumes voided at night, which in turn may be related to her greater fluid, caffeine, and alcohol consumption in the evening.

Routine urinary cytology is not helpful, but testing may be of value in women older than 50 years with irritative urinary tract symptoms, particularly if those symptoms are of sudden onset.

Postvoid Residual Volume

Incomplete bladder emptying may cause incontinence. Patients with a large postvoid residual urine volume (PVR) have a diminished functional bladder capacity because of the dead space occupied in the bladder by retained urine. This stagnant pool of urine also is a source of urinary tract infections because the major defense of the bladder against infection is frequent, nearly complete emptying.

A large PVR can contribute to urinary incontinence in two ways. If the bladder is overdistended, increases in intra-abdominal pressure can force urine past the urethral sphincter, causing stress incontinence. In some cases, bladder overdistention may provoke an uninhibited contraction of the detrusor muscle, leading to incontinence. These conditions may coexist, further complicating the problem.

The PVR can be assessed by either direct catheterization or ultrasonography. Although sufficiently accurate for clinical purposes, ultrasonography measurements of PVR have a standard error of 15% to 20%. Thus, assessment of the catheterized volume is preferred (36). It is important to perform this test within 10 minutes of a void to avoid an artificially

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elevated result because of diuresis. It is generally agreed that a PVR level less than 50 mL is normal and greater than 200 mL is abnormal, but there is much debate about values in the midrange. Because many women are unable to void well during an anxiety-ridden first visit, it is helpful to recheck the PVR at a future visit before embarking on further diagnostic tests. The value of assessing bladder emptying in neurologically normal women who do not have pelvic organ prolapse or symptoms of voiding dysfunction has not been demonstrated.

Cough Stress Test

Patients should be examined with a full bladder, particularly if stress incontinence is a consideration. Urine egress from the urethra at the time of a cough documents stress incontinence. If leakage is not observed when the woman is supine, she should stand with her feet separated to shoulder width and cough several times. **Many women with urge incontinence caused by detrusor overactivity may experience urine loss during a cough stress test, but this finding may not be relevant to their real symptom.** The physical findings must be set within the context of the patient's history to be relevant.

Pad Tests

Pad tests are widely used in patient-oriented research as an objective way of assessing treatment effectiveness, but rarely are they used in clinical practice. Pad tests, usually performed in women with a full bladder, quantify the volume of urine lost by weighing a perineal pad

before and after specified activities. Pad tests can be divided into short-term tests, usually performed under standardized office conditions, and long-term tests, usually performed at home for 24–48 hours. Pad tests are generally performed with a symptomatically full bladder or with a certain volume of saline instilled into the bladder before beginning the series of exercises. A pad weight gain of 1 or more grams is considered positive for a 1-hour test, and a pad weight gain greater than 4 grams is positive for a 24-hour test.

Advanced Testing

Urodynamics

At its most basic level, a urodynamic study is anything that provides objective evidence about lower urinary tract function (37). In this sense, measurement of a patient's voided urine volume and catheterization to determine her PVR are urodynamic studies. A frequency/volume chart is also a valuable urodynamic study. **Obtaining clinically valuable information does not always require the use of expensive, complex technology. After basic testing, further testing is recommended in the following circumstances: the diagnosis is uncertain (for example, because of major discrepancies between the history, the voiding diary, and symptom scales); surgery is being considered; or the patient has hematuria in the absence of an infection, an elevated PVR, a neurologic condition that may complicate treatment (such as multiple sclerosis), marked pelvic organ prolapse, or numerous prior surgical attempts at correction.** Current urodynamic definitions are summarized in Table 23.6.

Uroflowmetry

To assess voiding function, urodynamic testing usually begins with uroflowmetry, a study in which the volume of urine voided is plotted over time. Flow time, peak flow rate, and time to peak flow usually increase as the voided volume increases.

Filling Cystometry

Cystometrography (also termed *cystometry*) is done to assess bladder and urethral function during bladder filling. Simple (or single-channel) cystometry is performed

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when bladder pressure only is measured during filling. Because the bladder is an intra-abdominal organ, the pressure recorded in the bladder is a combination of several other pressures, most notably the pressure created by the activity of the detrusor muscle itself and the pressure exerted on the bladder by the weight of the surrounding intra-abdominal contents (e.g., uterus, intestines, straining, or exertion). For this reason, **the technique of complex (also called multichannel or subtracted) cystometry is generally used to try to approximate the actual pressure exerted in the bladder by the activity of the detrusor muscle alone. The detrusor pressure (P_{det}) is obtained by measuring total intravesical pressure (P_{ves}) with a bladder pressure catheter, approximating intra-abdominal pressure (P_{abd}) with a rectal or vaginal catheter, and then electronically subtracting the latter from the former:**

$$P_{det} = P_{ves} - P_{abd}$$

Measurements can be obtained using electronic microtip transducer pressure catheters, fluid-filled pressure lines, fiberoptic catheters, or air-charged catheters. All are acceptable for clinical use, but it is important to realize that when different types of catheters are used, the correlation between numbers is imperfect. Other technical factors that influence

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cystometry results include the choice of distending medium, filling rate, and patient position.

The steps involved in a multichannel urodynamic study are outlined in Table 23.7.

Normal cystometric values for women are shown in Table 23.8.

Table 23.6 Urodynamic Definitions

I. Bladder sensation	
A. First sensation	First becomes aware of bladder filling
B. First desire to void	Feeling that would lead the person to void at next convenient moment, but voiding can be delayed if necessary
C. Strong desire to void	Persistent desire to void without the fear of leakage
D. Sensation	classified as:
1.	Increased
2.	Reduced
3.	Absent
4.	Nonspecific bladder sensations (other symptoms make person aware of bladder filling, like abdominal fullness)
5.	Bladder pain (is abnormal)
6.	Urgency (sudden compelling desire to void)
II. Detrusor function	
A. Normal	Allows bladder filling with little or no change in pressure; no involuntary phasic contractions
B. Detrusor overactivity	Involuntary detrusor contractions during filling
1.	<i>Phasic</i> Characteristic wave form; may or may not lead to incontinence
2.	<i>Terminal</i> Single involuntary detrusor contractions occurring at cystometric capacity, which cannot be suppressed, and results in incontinence usually resulting in bladder emptying
3.	<i>Detrusor overactivity incontinence</i> Incontinence that is due to an involuntary leakage episode
4.	<i>Neurogenic detrusor overactivity</i> There is a relevant neurologic condition (replaces term <i>detrusor hyperreflexia</i>)
5.	<i>Idiopathic detrusor overactivity</i> No definite cause (replaces term <i>detrusor instability</i>)
C. Bladder compliance	Fill volume/change in detrusor pressure (P_{det})
1.	Calculate at start of bladder filling (usually 0)
2.	At cystometric capacity (excluding any detrusor contraction)
D. Bladder capacity	
1.	<i>Cystometric capacity</i> Volume at end of cystometrogram; capacity is volume voided together with any residual urine
2.	<i>Maximum cystometric capacity</i> Volume at which person feels she can no longer delay voiding

III. Urethral function

A. Normal urethral closure mechanism Maintains a positive urethral closure pressure during bladder filling

B. Incompetent urethral closure mechanism Allows leakage of urine in the absence of a detrusor contraction

C. Urethral relaxation incontinence Leakage that is due to urethral relaxation in the absence of raised abdominal pressure or detrusor overactivity

D. Urodynamic stress incontinence Involuntary leakage of urine during increased abdominal pressure, in the absence of detrusor contraction (replaces term *genuine stress incontinence*)

E. Urethral pressure (P_{ura}) Fluid pressure needed to open closed urethra

1. Pressure profile Pressure along length of urethra

2. Urethral closure pressure $P_{ura} - P_{ves}$

3. Maximum urethral closure pressure (MUCP) Maximum difference between P_{ura} and P_{ves}

4. Pressure transmission ratio Increment in urethral pressure on stress as percentage of simultaneously recorded increment in intravesical pressure

F. Abdominal leak point pressure Intravesical pressure at which urine leakage occurs because of increased abdominal pressure

IV. Pressure flow studies

A. Urine flow is defined as

1. Continuous

2. Intermittent

a. Flow rate Volume voided/unit time

b. Voided volume Total volume voided

c. Maximum flow rate

d. Voiding time Includes interruptions

e. Flow time Time over which measurable flow actually occurs

f. Average flow rate Voided volume/flow time

g. Closing pressure Pressure measured at end of measured flow

h. Detrusor function during voiding can be classified as:

1. Normal

2. Detrusor underactivity Contraction of reduced strength resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying

3. Acontractile Cannot be demonstrated to contract

i. Urethral function during voiding can be classified as:

1. Normal Continuously relaxed

2. Dysfunctional voiding Intermittent and/or fluctuating flow rate that is due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal people

3. Detrusor sphincter dyssynergia Detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle

4. Nonrelaxing urethral sphincter obstruction Usually occurs in people with a neurologic lesion

Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21: 167–178.

Table 23.7 Steps in Conducting a Multichannel Urodynamic Study

1. **Insert pressure and filling catheter into bladder** (may be two catheters or dual catheter) to measure intravesical pressure and to fill bladder. Insert pressure catheter into upper vagina or rectum to approximate abdominal pressure.
2. **Infuse fluid (usually sterile water or saline, sometimes radiographic contrast dye) at a rate of 50 to 100 mL/min.** Record the volume infused and the pressure measurements continuously. The patient's bladder may be filled with her lying supine, in a modified lithotomy position, sitting, or standing. When possible, do cystometry in the standing position as most patients with incontinence report this problem more when they are erect.
3. **Note the point at which any leakage occurs.**
4. **During filling, record the first desire to void (that is, the feeling that would lead her to void at the next convenient moment, but voiding can be delayed if necessary) and the strong desire to void (that is, the persistent desire to void without the fear of leakage).** The maximum cystometric capacity, in women with normal sensation, is the volume at which the woman can no longer delay micturition; filling should not be continued to the point of pain or severe discomfort.
5. **If no detrusor overactivity is noted during filling, have the patient do provocative maneuvers at maximum capacity, such as coughing, heel-bouncing, and listening to the sound of running water to provoke uninhibited detrusor contractions,** which may be the cause of the patient's symptoms.

An example of detrusor overactivity seen during complex cystometry is shown in Figure 23.5. Surface or needle electromyography may be performed during filling and voiding to assess muscle activity of the urethral sphincter or pelvic floor. Electromyography as generally performed has not been proved useful in neurologically intact women with symptoms of only stress urinary incontinence, and thus is not required in this patient population.

Both false-positive and false-negative results can occur with urodynamic studies.

False-positive results occur in patients with asymptomatic detrusor overactivity, detrusor overactivity that is irrelevant to the symptom, or detrusor overactivity that is situational (e.g., caused by test anxiety). False-negative results can occur with 20-minute cystometrography

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because this test is not always an accurate measure of daily bladder activity. Looking for detrusor instability with such a test is like looking for an episodic cardiac arrhythmia using 12-lead electrocardiography, as opposed to looking for the arrhythmia using a 24-hour Holter monitor. The sensitivity of the latter test is far greater than that of the former. Ambulatory urodynamics can be performed and are more likely to detect detrusor overactivity than office-based studies.

Table 23.8 Approximate Normal Values of Female Bladder Function

- Residual urine <50 mL
- First desire to void occurs between 150 and 250 mL infused
- Strong desire to void does not occur until after 250 mL
- Cystometric capacity between 400 and 600 mL
- Bladder compliance between 20 and 100 mL/cm H₂O measured 60 sec after reaching cystometric capacity
- No uninhibited detrusor contractions during filling, despite provocation
- No stress or urge incontinence demonstrated, despite provocation
- Voiding occurs as a result of a voluntarily initiated and sustained detrusor contraction
- Flow rate during voiding is >15 mL/sec with a detrusor pressure of <50 cm H₂O

From **Wall LL, Norton P, Delancey J.** *Practical urogynecology*. Baltimore, MD: Williams & Wilkins, 1993, with permission.

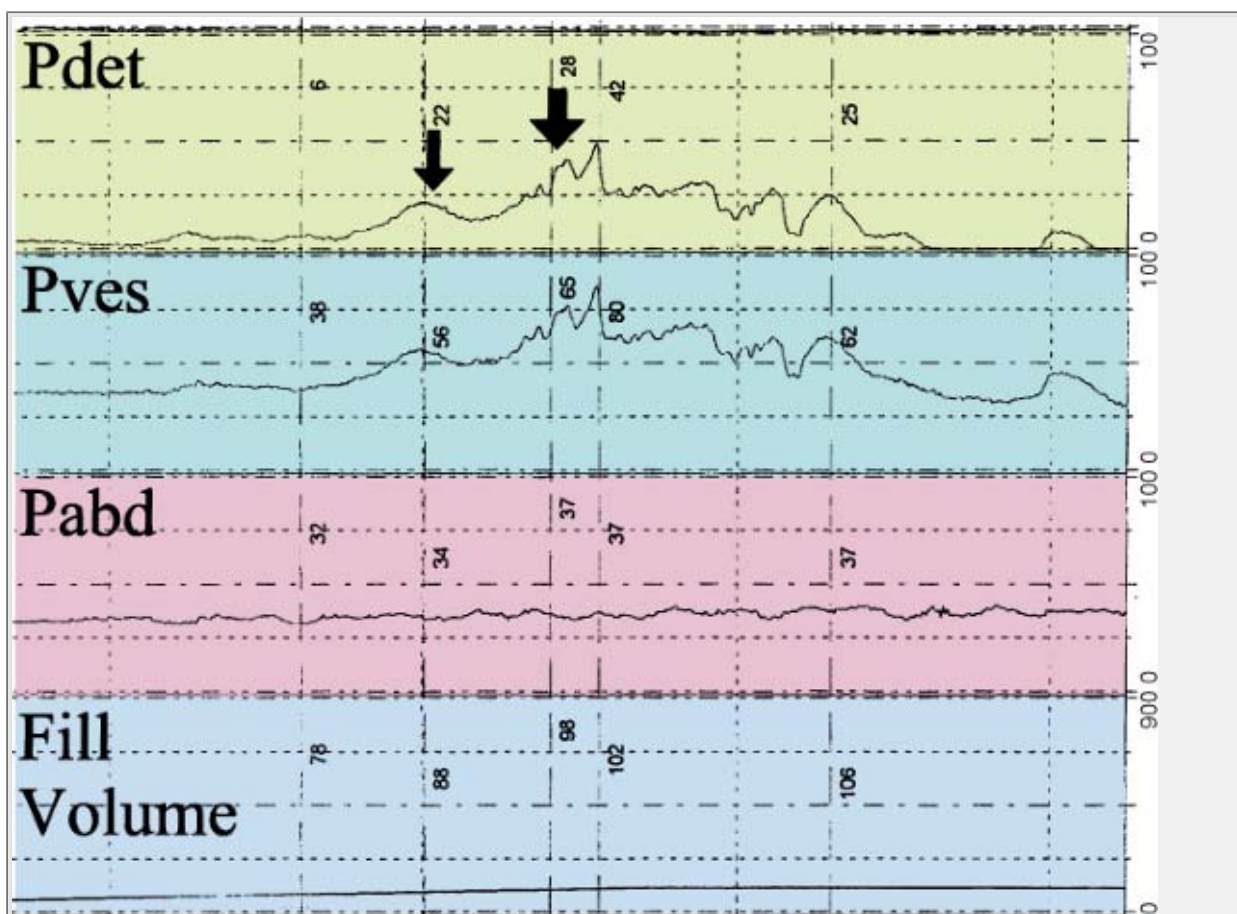


Figure 23.5 Detrusor overactivity on filling cystometrography. The patient begins to sense urgency, accompanied by an unstable bladder contraction, when 88 mL of water are instilled into the bladder. The detrusor pressure rises, and when 96 mL of water are instilled, she leaks. (P_{abd}, abdominal pressure; P_{ves}, vesical pressure; P_{det}, detrusor pressure)

Tests of Urethral Function

Several tests of urethral function, including urethral pressure profilometry, Valsalva leak-point pressures, and the fluoroscopic and cystoscopic assessment of the bladder neck, have been used to guide therapy in women with stress urinary incontinence. **Women with poor urethral function, evidenced by low Valsalva leak-point pressures, low maximal**

urethral closure pressures, or a visualized open bladder neck (Fig. 23.6), are thought to be at higher risk of treatment failure using standard retropubic urethropexy. Cutoff values for these tests are poorly defined and remain controversial. Although women with stress urinary incontinence have, on average, significantly lower maximal urethral closure pressures than those without incontinence, there is wide overlap in the values between such women, and no lower limit of urethral closure pressure has been established that predisposes women to stress urinary incontinence.

The urethral pressure profile is a test designed to measure urethral closure. Because continence requires the pressure in the urethra to be higher than the pressure in the bladder, it

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was believed that measuring the pressure differential between the two would provide useful clinical information. The urethral pressure profile is determined by slowly pulling a pressure-sensitive catheter through the urethra from the bladder.

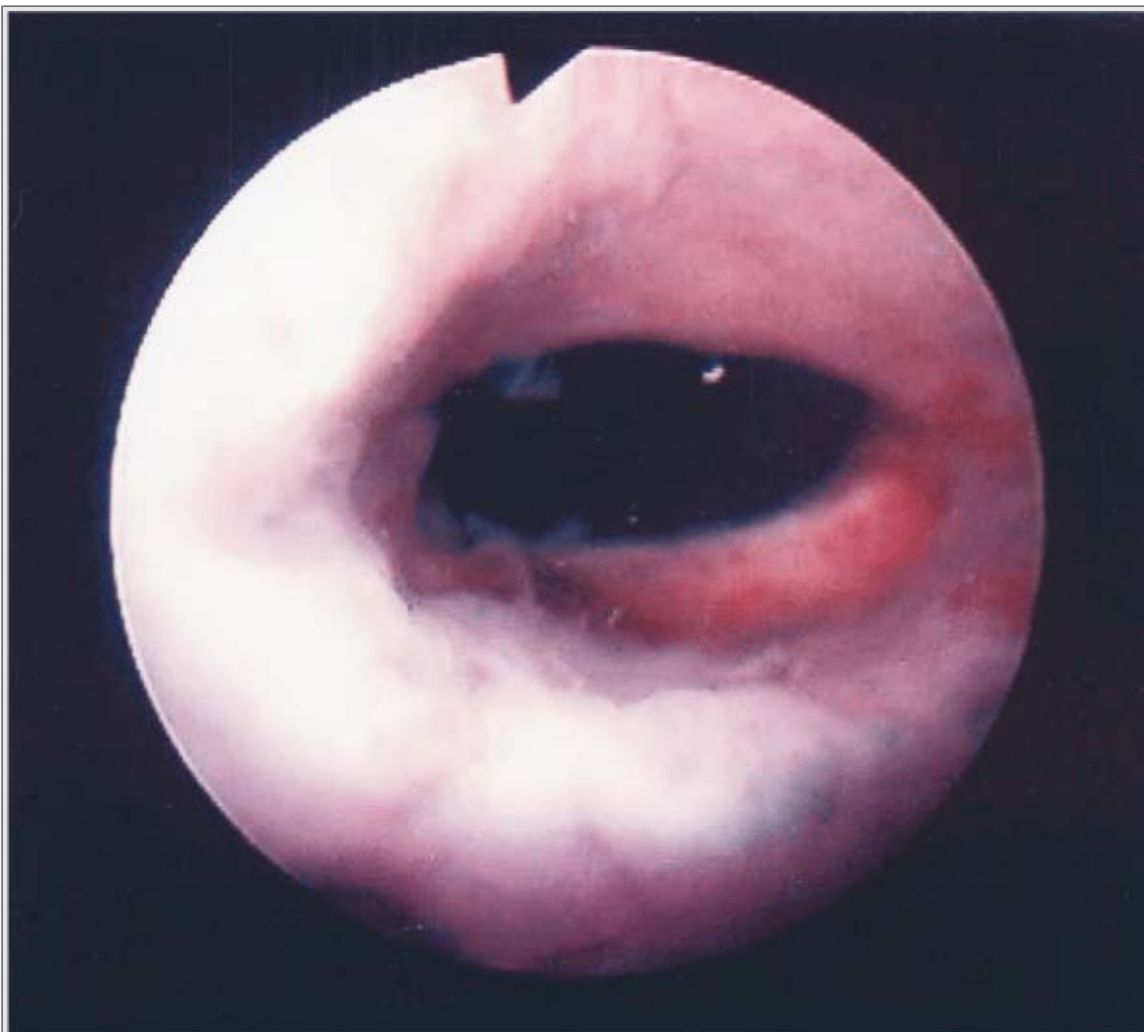


Figure 23.6 Open and scarred bladder neck in an elderly woman who has undergone three anterior colporrhaphies for stress urinary incontinence in the past.

The urethral closure pressure (P_{close}) is the difference between the urethral pressure (P_{ure}) and the bladder pressure (P_{ves}): $P_{\text{close}} = P_{\text{ure}} - P_{\text{ves}}$.

Although this pressure can be used to differentiate groups of normal women from groups of those with stress incontinence (women with stress incontinence tend to have higher urethral pressure levels than those who do not), there is considerable overlap between the

two groups. It has also been suggested that women with stress incontinence with low urethral closure pressure (<20 cm H₂O) have a poorer prognosis for surgical outcome than women who do not have this condition; however, this area has been the subject of considerable debate (3,38,39). Because stress incontinence, by definition, occurs during increases in intra-abdominal pressure that are generated by some kind of physical activity, it is not obvious why measurement of resting urethral pressure should be relevant to stress-related leakage, which is a dynamic event. One review concluded that urethral pressure profilometry is not a useful diagnostic test for stress incontinence in women and that its use in clinical management is unsupported by current evidence (40).

Leak-point pressure (LPP) is a urodynamic measure of the minimum intra-abdominal or intravesical pressure required to cause incontinence during abdominal strain or cough. There is no consensus about whether it should be measured from the resting supine baseline (generally near 0) or from the standing resting baseline (which increases

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depending on body mass). Other factors that may affect the results include the catheter's type, caliber, and placement (vaginal, rectal, or intravesical), the bladder volume at which the measurement is obtained, the mechanism by which intra-abdominal pressure is increased (coughing versus straining), and patient position (41).

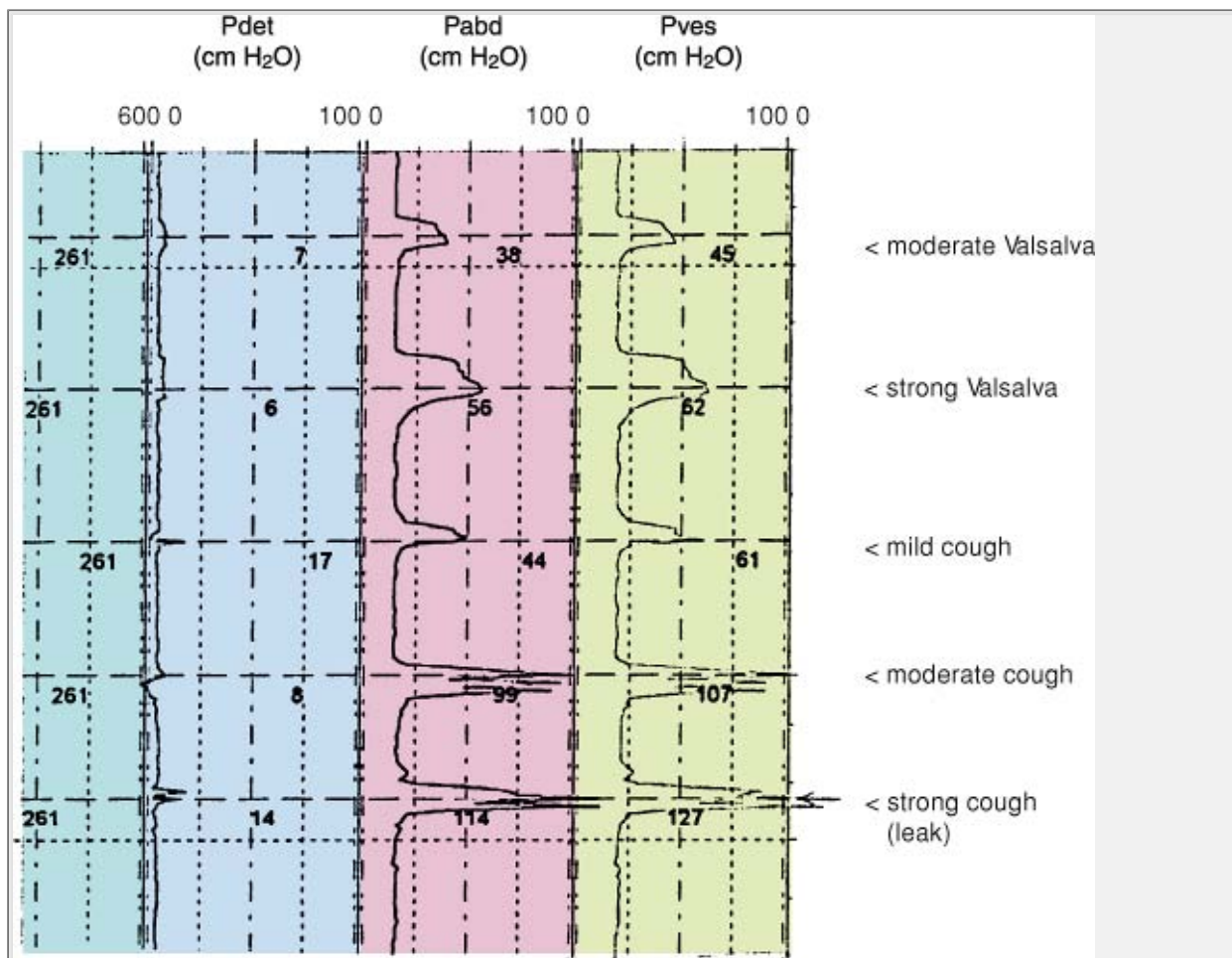


Figure 23.7 Leak point pressure. The abdominal leak point pressure (LPP) is 114 cm H₂O (the abdominal pressure at which the patient leaked urine).

Leak point pressure measurements often are performed at a bladder volume of 200 or 300 mL. Patients are asked to cough with gradually increasing force (cough leak-

point pressure) and finally to strain slowly (Valsalva) to increase intravesical pressure gradually. The lowest pressure at which leakage occurs is recorded as the cough or the Valsalva leak-point pressure (Fig. 23.7). If leakage is not demonstrated, the highest pressure that has been obtained can be recorded with the notation "no leakage" to the specified pressure as measured in cm H₂O. Currently, many clinicians use a cutoff point of 60 cm water pressure to separate women who have intrinsic sphincter deficiency from those who do not. This is problematic for two reasons: (i) the marked variability of results that depend on all the aforementioned factors, and (ii) the lack of prospective studies that demonstrate the predictive value of leak point pressure values on surgical outcomes. Results from this and other urodynamics tests must be evaluated as one piece of the patient's puzzle, along with the history, physical examination, voiding diary and other tests. Current Medicare guidelines require that when bulking agents, such as collagen, are considered to treat stress incontinence, the intra-abdominal leak point pressure when the bladder has been filled with at least 150 mL of fluid must be less than 100 cm H₂O.

Fluoroscopy and cystourethroscopy have both been used to visualize the bladder neck because many clinicians and investigators believe that a closed bladder neck is important in maintaining continence. However, studies of continent women reveal that many individuals with normal urethral function show evidence of bladder neck opening with physical stress

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(42). Neither test is recommended in the routine evaluation of women with straightforward incontinence.

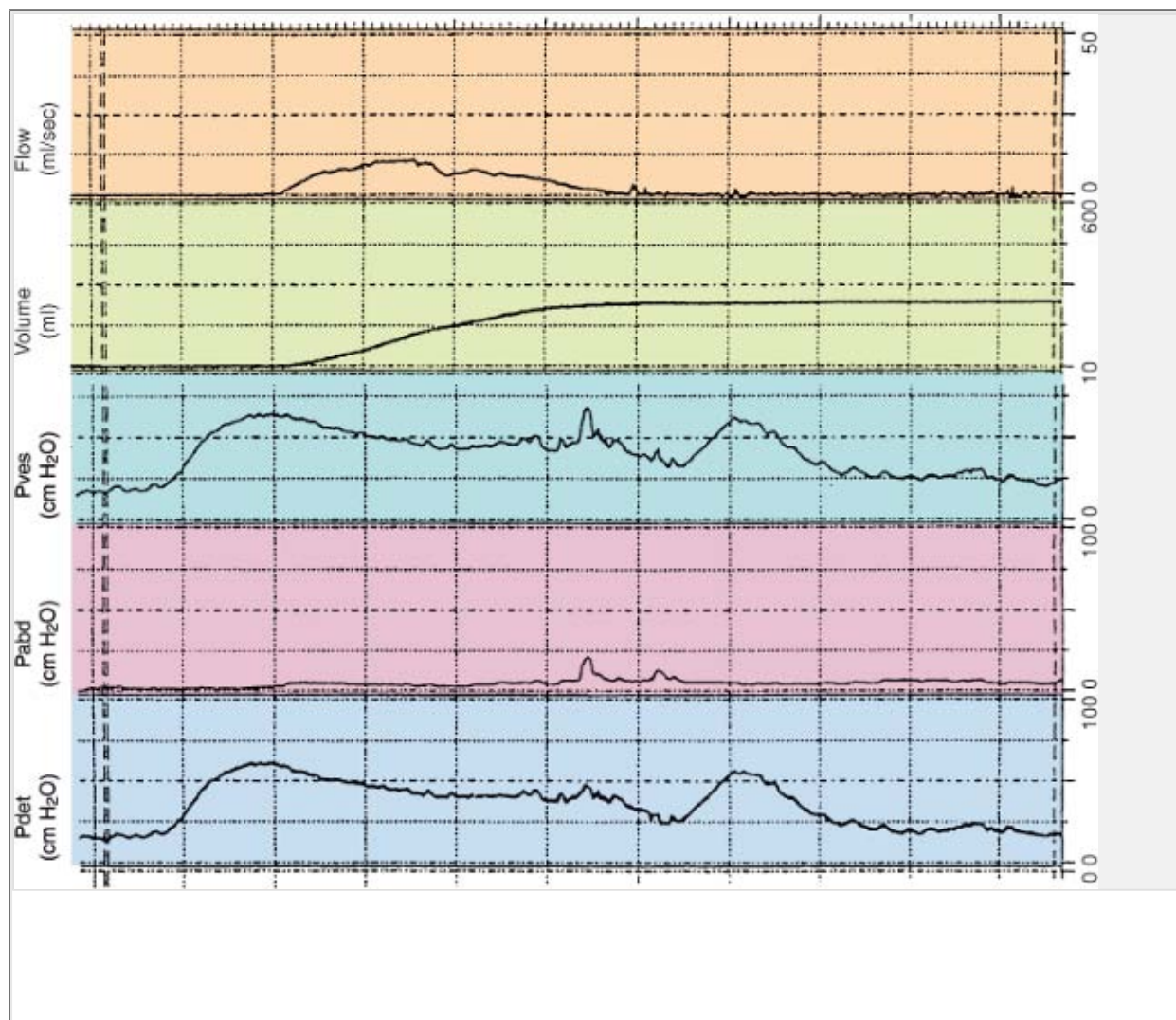


Figure 23.8 Voiding cystometrogram. This patient voids in an uninterrupted flow pattern by means of a prolonged bladder contraction. She does not strain to void, with the exception of minimal straining toward the end of the flow.

Voiding Cystometrography

Urodynamic testing usually concludes with an instrumented voiding study (also known as a pressure–flow study or voiding cystometrography), in which the vesical, abdominal, and urethral pressures are measured simultaneously during bladder emptying (Fig. 23.8). Various studies have identified Valsalva voiding, low preoperative flow rate, and high preoperative detrusor pressures during voiding as risk factors for postoperative voiding dysfunction; however, findings often are contradictory.

Imaging Tests

The role of imaging techniques in studying female urinary incontinence has not yet been established. Researchers are evaluating the potential roles of ultrasonography, fluoroscopy, functional neuroimaging, and magnetic resonance imaging (MRI). These tests should not be done routinely but are useful in certain conditions. If the patient's symptoms (easily remembered by the 3 Ds: dysuria, dribbling, and dyspareunia) or examination suggest a urethral diverticulum, MRI is the test of choice (43).

Neurophysiologic Tests

The neuromuscular function of the pelvic floor is dependent on the integrity of the nervous system. Injury can theoretically occur anywhere along these nerves, from the cell

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body located in Onuf's nucleus in the ventral part of the spinal cord, along its axon, to the neuromuscular junction. Pelvic floor neurophysiology utilizes techniques applied to nerves and skeletal muscles elsewhere in the body to document neuromuscular integrity or evidence of injury. Currently, these tests are not routinely used in the clinical evaluation of most incontinent women.

Pudendal Nerve Terminal Motor Latency

The pudendal nerve terminal motor latency (PNTML) indirectly assesses the integrity and patency of the terminal portion of the pudendal nerve, its neuromuscular junction, and the muscle it serves. Using a specialized electrode affixed over the index finger, the pudendal nerve is electrically stimulated near the ischial spine (either transrectally or transvaginally), and the resulting muscular response is measured. The response, termed a *compound muscle action potential (CMAP)*, is detected at the anal sphincter. The interval between the stimulation and the onset of the CMAP is measured. A prolonged latency is noted with injury to large and heavily myelinated axons. The latency time may be within the normal range when only smaller nerve fibers have been affected; thus, neurological dysfunction may exist in the presence of a normal latency time.

Sacral Reflexes

Only the distal efferent arm of the pudendal nerve is analyzed in the PNTML. Similar to the clinically obtained anal wink or bulbocavernosus reflex, electrically induced sacral reflexes can

gather information about both the afferent and efferent arc in the pelvic nerves. A short train of dual impulses delivered next to the clitoris and measured at the anal sphincter is termed the clitoroanal reflex and provides information about the integrity of the afferent and efferent arm of the somatic pudendal nerve. A stimulating electrode placed in the bladder sends these signals along the visceral, autonomic fibers to the spinal cord, and a reflex signal will return along the pudendal nerve to the anal sphincter.

Somatosensory Evoked Potentials

Normal pelvic floor and pelvic organ function ultimately is controlled by higher centers in the central nervous system, including the cerebral cortex. Recording electrodes located on the scalp near the motor cortex allow the signal transmission speed between a skeletal muscle and the brain to be measured. Repeated electrical stimuli, called *somatosensory evoked potentials*, at a muscle of interest are used to assess the integrity of the central afferent limb. In a reverse fashion, electrical or magnetically induced stimuli can be delivered at the motor cortex (or along the spine), and the induced muscle action potentials can be detected. Prolonged latencies not attributable to the peripherally studied nerves (such as with a PNTML or sacral reflex) are evidence of a central nervous system conduction flaw.

Electromyography

Electromyography (EMG) assesses the inherent electrical potentials generated during neuronal activation of skeletal muscle. It can be performed using surface electrodes or needle electrodes. Surface EMG measures the summation of muscle activity in the general area of the applied electrode. It is best used for simply describing the pattern and coordination of muscle activity, but is less useful in providing more specific assessments. Needle EMG of the pelvic floor can "map" the anatomic location of muscles but has largely been replaced by ultrasonography. The major value of needle EMG is its ability to assess nerve injury and determine whether the injury is acute and ongoing or chronic. Single-fiber EMG can quantify the ratio of muscle fibers to nerve fibers (the so-called fiber density). An increase in fiber density is evidence of previous nerve injury with successful reinnervation. Concentric needle EMG is more widely available and allows for further neurophysiologic evaluation. Abnormal electrical activity associated with acute injury may be seen, and

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motor unit action potentials (MUAPs) can be assessed and quantified. Following nerve injury and reinnervation, MUAP parameters—such as duration, amplitude, number of phases, and turns—are typically larger. Finally, the ability of a muscle to increase the firing frequency of motor neurons and the ability to recruit more motor neurons can also be assessed using this needle.

Nonsurgical Treatment

Treatment of urinary incontinence can be either nonsurgical or surgical. The approach to treatment is based on the clinical findings and the degree of discomfort experienced by the patient, who should be fully informed of the risks and expected outcome.

Lifestyle Changes

Lifestyle interventions can decrease stress urinary incontinence in many women (44). Weight loss in both morbidly and moderately obese women decreases leakage, and ways to incorporate this intervention in a management plan are being investigated. Postural changes (such as crossing the legs during periods of increased intra-abdominal pressure) often prevent stress urinary incontinence. There is some evidence that decreasing caffeine

intake improves continence; however, fluid intake in general seems to play a minor role in the pathogenesis of incontinence. Although smokers are at greater risk for incontinence, no data have been reported on whether smoking cessation resolves incontinence.

Physical Therapy

Medical evidence from well-designed randomized clinical trials shows that supervised pelvic floor muscle training (Kegel exercises) is an effective treatment for stress urinary incontinence.

The Cochrane Incontinence Group concluded that pelvic floor muscle training is consistently better than no treatment or placebo treatment for stress incontinence and should be offered as first-line conservative management to women. Intensive training sessions that include personal contact with a health care professional to teach and supervise pelvic floor muscle training may be more beneficial than standard care.

Biofeedback provides no added benefit over pelvic floor muscle training alone in women with stress urinary incontinence (45).

Several factors improve the likelihood that pelvic muscle training will relieve stress urinary incontinence. The woman must do the exercises correctly, regularly, and for an adequate duration. Based on exercise training of skeletal muscles elsewhere in the body, many physical therapists recommend training sessions three to four times per week, with three repetitions of eight to ten sustained contractions each time.

Electrical stimulation therapy has been used to treat incontinence by delivering low levels of current via a probe placed in the vagina or rectum. When compared with sham devices and pelvic floor exercises, electrostimulation has produced mixed results in the treatment of stress urinary incontinence (46,47) but may be more helpful in women with overactive bladders (48,49). Further research is needed to determine what niche this treatment may fill for women with urinary incontinence.

Behavioral Therapy and Bladder Training

Bladder training focuses on modifying bladder function by changing voiding habits. Behavioral therapy focuses on improving voluntary control rather than bladder function (50). The key component to bladder training is a scheduled toileting program. After reviewing the patient's voiding diary, an initial voiding interval is chosen that represents the longest interval between voiding that is comfortable. She is then instructed to empty her bladder when she awakes, and then every time during the day that the interval is reached (for example, every 30 to 60 minutes). When patients feel the urge to void during that interval, they are instructed to use urge-suppression strategies, such as distraction or

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relaxation techniques, until they get to the stated interval. Effective distraction strategies include mental exercises (such as mathematical problems), deep breathing, or "singing" the words to a song silently. The main goal is to avoid running to the bathroom at the moment of severe urgency. Another strategy is to quickly contract the pelvic muscle several times in a row ("freeze and squeeze"), which often lessens urgency. Gradually, the interval is increased (usually weekly), until the patient voids every 2 to 3 hours. Bladder training is most effective when women record every void and check in (by telephone or in person) with a health care provider weekly. Generally this program lasts for about 6 weeks. Bladder training is effective; in a trial in which bladder training was compared with treatment with *oxybutynin*, 73% of women in the bladder training group were clinically cured (51).

The primary technique of behavioral training is pelvic floor muscle training, as

described previously, but with a focus on urge inhibition. Mastering voluntary pelvic floor muscle contractions helps to strengthen the outlet (decreasing leakage) and inhibit detrusor contractions. Other components of therapy may include voiding schedules, urge-inhibitions strategies, and fluid management.

Patients with neurogenic detrusor overactivity, rather than idiopathic detrusor overactivity, do not respond as well to behavioral therapy because the problem is actually one of neural pathway destruction rather than the need to re-establish cortical control mechanisms. Frequently, these patients have a trigger volume of urine that sets off a contraction that they cannot control voluntarily. They may benefit from a timed schedule in which they void at regular intervals (such as every 2 hours) to keep their bladder volume below the trigger point. Attempting to lengthen the interval between voids does not often work well.

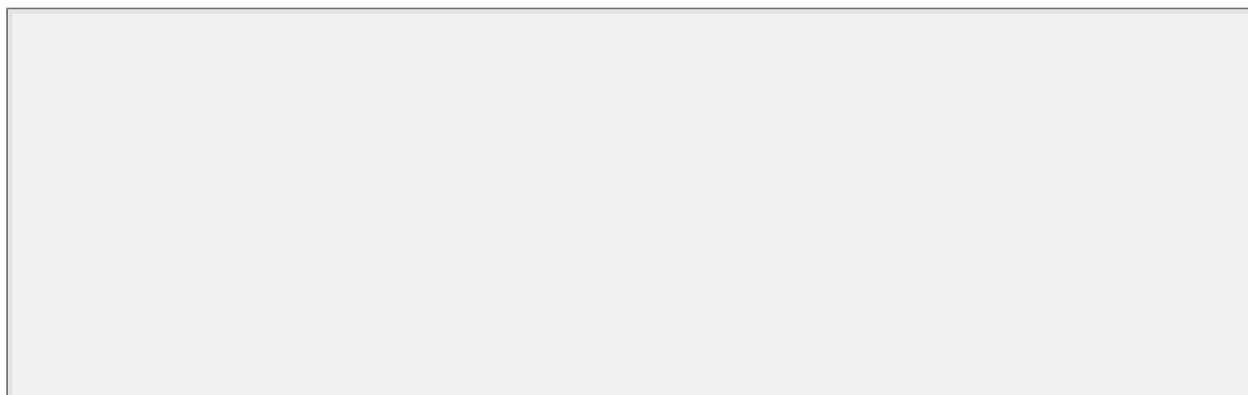
Less-intensive treatments also decrease incontinence episodes. In a randomized trial, a simple self-help booklet was only somewhat less effective in reducing leakage (mean reduction in leakage episodes 43%) than behavioral training (mean reduction 69%) or behavioral training plus electrical stimulation (mean reduction 72%) (52).

Vaginal and Urethral Devices

Vaginal devices (pessaries) and urethral inserts are available for treating stress urinary incontinence. There are no long-term randomized trials comparing devices and other treatments, but devices appear to be an acceptable treatment for some women. In a tertiary care population, approximately two thirds of women with stress urinary incontinence offered a trial of vaginal devices chose to undergo pessary fitting (53). Most (89%) achieved a successful fit. Of those that took a pessary home to manage their stress urinary incontinence, approximately one half used it for more than 6 months. Women who stopped using the pessary generally did so within the first month. Some women are pleased to be able to avoid surgery, or to use a "crutch" while waiting for the effect of pelvic muscle training; others prefer a treatment option (like surgery) that doesn't require daily intervention. Examples of some vaginal devices are shown in Figure 23.9.

Urethral inserts are sterile inserts placed into the urethra by the patient and removed before a void, after which a new sterile insert is reinserted. Such inserts are appropriate for women with relatively pure stress incontinence, no history of recurrent urinary tract infections, and no serious contraindications to bacteriuria (e.g., artificial heart valves).

Devices that were once marketed in the United States and may be available again include a single-use triangularly shaped foam device with an adhesive hydrogel (54) that adheres to the perimeatal area to keep urine from exiting the urethral meatus, and a hat-shaped silicone patch (55) that adheres by applying an adhesive gel to the edge of the device, squeezing the central dome, and creating a vacuum. The patch can be reapplied after voids and reused for up to 1 week.



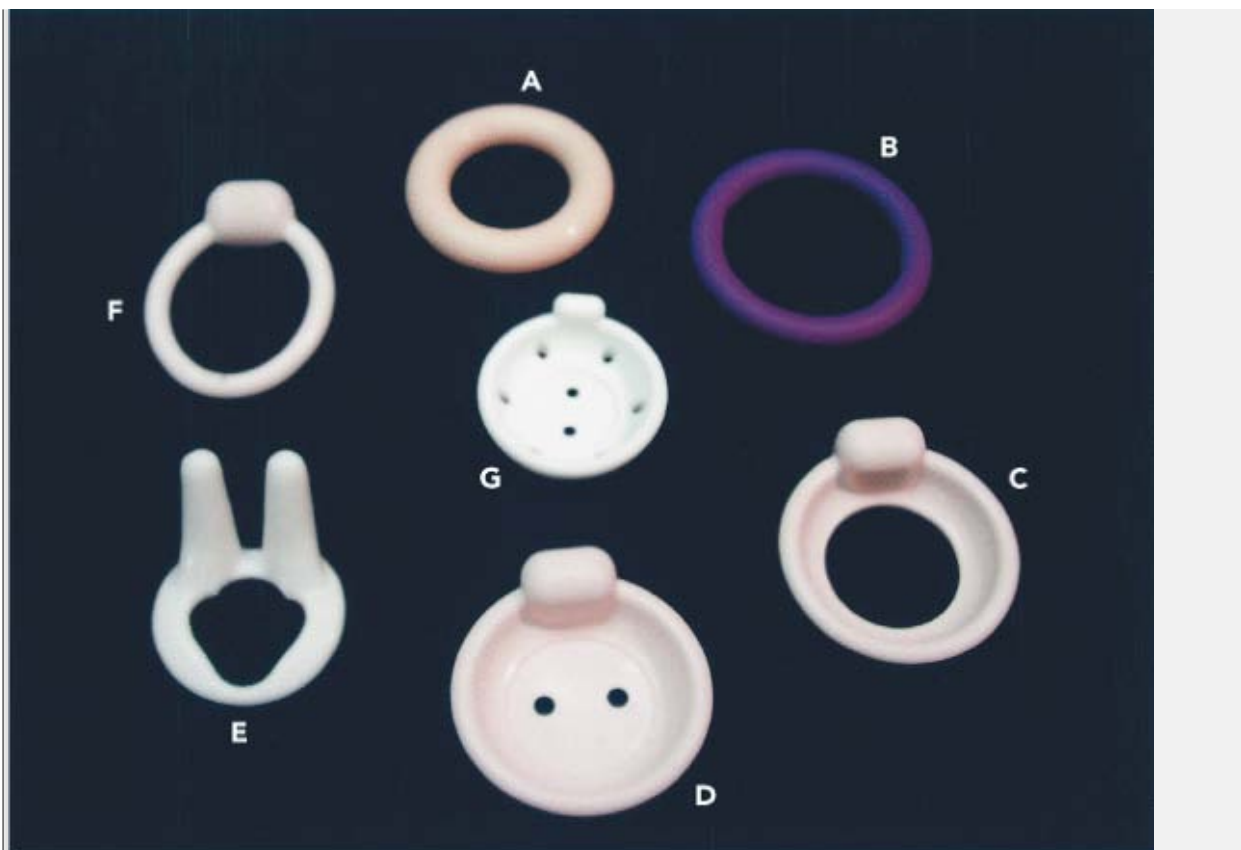


Figure 23.9 Vaginal incontinence pessaries: (clockwise from top): A: Suarez ring (Cook Urological, Spencer, IN), B: PelvX ring (DesChutes Medical Products, Bend, OR), C: Incontinence dish (Milex Inc., Chicago, IL), D: Incontinence dish with support (Mentor Corporation, Santa Barbara, CA), E: Introl prosthesis (was Johnson and Johnson; currently not available), F: Incontinence ring with support (Milex Inc., Chicago, IL), (middle): G: Incontinence dish with support (Milex Inc., Chicago, IL).

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Medications

Stress Incontinence

The tone of the urethra and bladder neck is maintained in large part by α -adrenergic activity from the sympathetic nervous system. For this reason, many pharmacologic agents have been used with varying degrees of success to treat stress incontinence. These drugs include *imipramine* (which has a concomitant relaxing effect on the detrusor), *ephedrine*, *pseudoephedrine*, *phenylpropanolamine*, and *norepinephrine*. Unfortunately, many of these compounds also increase vascular tone and may, therefore, lead to problems with hypertension, a condition that afflicts many postmenopausal women with stress incontinence. These effects may preclude the use of α -agonists in such patients. A recent U.S. Food and Drug Administration (FDA) statement urged caution in the use of *phenylpropanolamine*, an α -agonist, in women because of an apparent increased epidemiologic risk for hemorrhagic cerebral vascular accidents. Although the risk remains very low, it is not possible to predict who is at risk for this complication (56). The use of these agents in the treatment of stress urinary incontinence appears to be more limited than originally thought (57).

Based on a biologic rationale, it was thought that estrogen could effectively treat

urinary incontinence given the presence of estrogen receptors in the bladder, urethra, and levator muscles. In early uncontrolled case series, women using various estrogen preparations experienced less incontinence. However, more recently, in several large randomized trials,

women assigned to receive estrogen and progesterone not only did not have less leakage, but in fact were more likely to experience the onset of incontinence or worsening of baseline symptoms (58). In 23,296 women enrolled in the Women's Health Initiative double-blind, placebo-controlled, randomized clinical trial, use of menopausal hormone therapy (*conjugated estrogen* alone in women with a prior hysterectomy, *conjugated estrogen* and *medroxyprogesterone acetate* in women with a uterus) increased the incidence of all types of urinary incontinence at 1 year among women who were continent at baseline (59). Among women who reported urinary incontinence at baseline, both frequency and severity of incontinence worsened at 1 year in women taking either hormone preparation compared with those in the placebo group. Thus, **conjugated estrogen with or without progestin should not be prescribed for the prevention or relief of urinary incontinence.**

Serotonin and norepinephrine reuptake inhibitors (SSRIs) are being investigated for their role in treating stress urinary incontinence but currently are not available for this indication. In a multicenter, double-blind, placebo-controlled randomized trial, there was an 18% to 23% net difference in the percent reduction in incontinence episode frequency comparing *duloxetine chloride* 40 mg/day (59% reduction) and 80 mg/day (64% reduction) with placebo (40% reduction) after a 12-week treatment period (60). Other investigators have also found a high response rate in women assigned to placebo. This is partly due to the intensity of research protocols (which require paying more attention to one's bladder than usual) but also speaks to the potential therapeutic role of simply completing the voiding diary.

Urge Incontinence and Overactive Bladder

The drugs used for treating detrusor overactivity can be grouped into different categories according to their pharmacologic characteristics; however, for all practical purposes, **these drugs are anticholinergic agents that exert their effects on the bladder by blocking the activity of acetylcholine at muscarinic receptor sites.** All of these drugs have side effects, the most common of which are dry mouth resulting from decreased saliva production, increased heart rate because of vagal blockade, feelings of constipation resulting from decreased gastrointestinal motility, and occasionally, blurred vision caused by blockade of the sphincter of the iris and the ciliary muscle of the lens of the eye. Other drugs, such as *imipramine*, may produce orthostatic hypotension and cardiac arrhythmias.

Current medications commonly used to treat these conditions are listed in Table 23.9. The introduction of several new drugs for overactive bladder has resulted in significant attention being given to urinary incontinence in the media (61,62,63,64,65,66,67,68).

The newer drugs have some advantages over *oxybutynin*, which has been available for decades. These advantages include once- (or sometimes twice-) daily dosing, rather than three to four times per day and, to some degree, a less severe side-effect profile. The latter is due to changes in the delivery system and to more selectivity of muscarinic receptors (so that, for example, the bladder may be targeted more than the salivary glands). In addition, quaternary amines (such as trospium chloride) are not distributed into the central nervous system because of their large molecular size and hydrophilicity. The primary disadvantage of the newer agents is cost. Head-to-head trials of many of these newer drugs (sponsored by the drug manufacturers) have been carried out and generally show favorable results for the newer preparations with respect to the comparison drugs. **In general, in these large**

randomized trials, the drug reduces incontinence episodes by 50% to 70%, whereas placebo reduces incontinence episodes by 40% to 60%. Clinicians must carefully assess whether statistically significant changes in incontinence episodes or frequency translate into clinically significant ones. **A review of one newly**

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released agent concluded that, "None of these drugs are as effective as advertisements to the public have suggested" (69).

Table 23.9 Commonly Used Medications for Urge Incontinence	
Drug	Oral Dose Range
Generic and Brand Names	
Oxybutynin	
<i>Ditropan</i> ^a	2.5–5 mg tid–qid
<i>Ditropan syrup</i>	1 tsp (5 mg)
<i>Ditropan XL</i> ^b	5, 10, or 15 mg qd
<i>Oxytrol patch</i> ^c	1 patch 2 times per week
Hyoscyamine	
<i>Levsin</i> ^d	0.125–0.25 mg qid
<i>Levbid, Levsinex</i>	1 tab bid
<i>Levsin elixir</i>	1 tsp (0.25 mg qid)
<i>Levsin/SL</i>	sublingual pill
<i>Cystospaz</i> ^e	0.15–0.3 mg qid
<i>Cystospaz-M</i>	1 tab bid
Dicyclomine	
<i>Bentyl</i> ^a	20 mg qid
Probantheline	
<i>ProBanthine</i> ^f	15–30 mg qid
Tolteridene	
<i>Detrol</i>	1–2 mg bid (immediate release)
<i>Detrol LA</i> ^g	4 mg qd (extended release)
Tropium chloride ^h	
<i>Sanctura</i>	20 mg bid
Solifenacin succinate ⁱ	
<i>Vesicare</i>	5–20 mg qd (one daily dose; usual dosing is 5–10 mg qd)

tid, three times a day; qid, four times a day; qd, every day; bid, twice a day.

^a Hoeschst Marion Roussel, Kansas City, MO; ^b Alza Corporation, Mountain View, CA; ^c Watson Pharma, Inc., Morristown, NJ; ^d Schwartz Pharma, Inc., Milwaukee, WI; ^e PolyMedica Pharmaceuticals, Woburn, MA; ^f Roberts Pharmaceutical Corp., Eatontown, NJ; ^g Pharmacia & Upjohn, Kalamazoo, MI; ^h Odyssey Pharmaceuticals, East Hanover, NJ; ⁱ Yamanouchi Pharma Ltd., Surrey, UK.

When initiating therapy with generic oxybutynin, it is best to start with a lower dose (particularly for elderly patients) and increase it as needed to a higher, more frequent dosage. Patients should be encouraged to titrate their medication to their symptoms and to vary the dosage (within acceptable limits) according to their needs. If this is not effective, the next step is to move to one of the other anticholinergic agents. Some women may respond better to one agent than another. A 2-week trial is sufficient to determine effectiveness. It is helpful to ask patients to record daily episodes of incontinence or urgency before and during therapy so effectiveness can be more accurately determined.

Patients should be warned of the side effects of anticholinergic agents. Patients should be particularly advised about the symptom of a dry mouth and told that this is not due to thirst. Some patients increase their fluid intake to combat this problem, with a subsequent worsening of their incontinence. If dry mouth is a problem, patients should relieve it by chewing gum, sucking on a piece of hard candy, or eating a piece of moist fruit.

Nocturia and Nocturnal Enuresis

Medications that treat nocturia and nocturnal enuresis generally have one of three aims: to reduce urine output, to increase bladder capacity and reduce unstable bladder contractions, and to act centrally on sleep and micturition centers.

An analog of arginine vasopressin, DDAVP, has been used extensively to treat children with nocturnal enuresis. Some studies suggest that it may also be useful in adults (70,71). It is available both as a nasal spray and as an oral preparation. When taken orally, the dose required is approximately 10 times greater because of the increased availability of the nasal preparation. Complications associated with the DDAVP include hyponatremia, particularly in patients with excessive fluid intake; therefore, it is essential in higher-risk patients to measure serum sodium levels periodically.

There are few clinical trials that specifically investigate the use of anticholinergic medications to treat nocturia or nocturnal enuresis. Anecdotal evidence supports a trial of a long-acting or extended-release form of an anticholinergic, taken approximately 1 hour before bedtime.

The most extensively studied medications for the treatment of nocturnal enuresis are tricyclic antidepressants, particularly imipramine. These agents may work by altering sleep mechanism, by providing anticholinergic or antidepressant effects, or by affecting antidiuretic hormone excretion. The typical starting dose of *imipramine* is 25 mg at bedtime, which may be increased to as high as 75 mg. In the elderly, *imipramine* should be used cautiously because it increases the risk of hip fracture, presumably related to the potential side effect of orthostatic hypertension (72).

In a randomized, placebo-controlled study comparing nighttime doses of placebo and 1 mg of *bumetanide* (a loop diuretic), *bumetanide* decreased nocturia episodes by 25% compared with placebo (73). Patients who produce half of their total urine at night often benefit from the use of a diuretic (e.g., 20 mg *furosemide*) in the late afternoon to move fluid through the system and decrease their nighttime urine production.

Surgical Treatment for Stress Incontinence

In a systematic review of 943 citations, only 76 (11 randomized trials, 20 prospective cohort studies, and 45 retrospective cohort studies) met minimum criteria that the investigators set for reporting results of surgical trials or series (74). The median follow-up interval was short: 1 year for prospective studies and 2 years for retrospective studies. None of the studies at that time described quality-of-life considerations, and few studies obtained the patient's perception on outcome in a standardized fashion. Of the 31 prospective studies, 28 were single center, and 29 were limited to teaching hospitals. As a result, the ability to generalize the findings was questionable. Although current studies generally do include instruments for measuring the impact of the surgery on the patient's quality of life, most published studies continue to represent the short-term experience of surgeons from one site.

In 1997, the American Urological Association convened a clinical guidelines panel to analyze published outcomes data on surgical procedures to treat female stress urinary incontinence and to produce practice recommendations to guide surgical decision-making (56,75). **The panel concluded that colposuspensions (e.g., Burch, Marshall-Marchetti-Krantz [MMK]) and slings were more effective than transvaginal needle suspensions or anterior repairs for long-term success (48 month cure/dry rates). The median probability estimates for cure/dry rates at 48 months and longer were 84% (95% CI, 79%–88%) for colposuspensions and 83% (95% CI, 75%–88%) for sling procedures, compared with 67% (95% CI, 53%–79%) for transvaginal needle suspensions and 61% (95% CI, 47%–72%) for anterior repairs.**

Historical Perspective

Anterior vaginal repair (also termed *anterior colporrhaphy*) was described by Howard Kelly in 1914, and this operation remained the standard first approach to stress incontinence until the middle of the twentieth century (76). Many different operations have been lumped together under the term *anterior colporrhaphy*, including simple plication of the bladder neck, elevation of the bladder neck by plicating the fascia under the urethra, and elevation and fixation of the bladder neck by passing sutures lateral to the urethra and driving the needles anteriorly into the back of the pubic symphysis for fixation. As noted previously, the problem with most techniques of anterior colporrhaphy is that they do not hold up well over time (77,78,79). In essence, this operation attempts to take weak support from below and to push it back up from below, with hope that these structures will maintain their strength and position over time. Although there have been excellent long-term results shown with anterior colporrhaphy, most of these cases involve specific techniques requiring skillful dissection of the endopelvic fascia, deep bold bites of suture, and fixation of permanent sutures to the pubic bone from below: in essence, a transvaginal retropubic bladder neck suspension (80,81). Most surgical series that have evaluated techniques of anterior colporrhaphy for stress incontinence show long-term success rates of only 35% to 65%, a figure that most would regard as unacceptably low. **Anterior colporrhaphy should be reserved primarily for patients requiring cystocele repair who do not have significant stress incontinence.**

Needle suspension procedures are so named because they suspend the urethra and bladder neck through a technique that involves passage of sutures between the vagina and anterior abdominal wall using a specially designed long needle carrier. To perform these operations, a vaginal incision is typically made at the level of the bladder neck, the endopelvic fascia is perforated, the space of Retzius is entered from below, and a permanent suture is passed down through a low abdominal incision through the retropubic space, where it is fixed to the endopelvic fascia at the level of the bladder neck. The long needle is then passed back up through the retropubic space to the abdominal incision, where it is tied in place. The first needle suspensions were performed by a gynecologist, Dr. Armand Pereyra, in the 1950s, but many urologic surgeons have since modified the technique (82,83,84,85,86,87). These procedures are relatively simple and take less time to perform than open procedures, but this advantage is offset by the fact that they are not as effective in curing stress incontinence. **Although initial cure rates are between 70% to 90%, rates decrease significantly over time in many series, with 5-year success rates of 50% or less (88,89,90,91,92,93). Therefore, these operations are also falling out of favor.**

Retropubic Urethropexy (Colposuspension)

The modern era of retropubic surgery for stress incontinence began in 1949, when

Marshall, Marchetti, and Krantz described their technique for urethral suspension in a man with post prostatectomy incontinence (94). Since that time, a variety of modifications of this operation have been described, all of which share at least two characteristics: They are performed through an open low abdominal incision or with laparoscopically assisted exposure of the space of Retzius, and they all involve attachment of the periurethral or perivesical endopelvic fascia to some other supporting structure in the anterior pelvis (Fig 23.10). In the MMK operation, the periurethral fascia is attached to the back of the pubic symphysis. Another approach, the Burch colposuspension, involves the attachment of the fascia at the level of the bladder neck to the iliopectineal ligament (Cooper's ligament) (95,96). With the paravaginal repair, the lateral endopelvic fascia along the urethra and bladder is reattached to the arcus tendineus fascia pelvis (97,98). In the Turner–Warwick vagino–obturator shelf procedure, the endopelvic fascia, vagina, or both are attached to the fascia of the obturator internus muscle (99,100). All of these operations aim to correct anatomic hypermobility of the urethra and bladder neck. **The long-term success rate for patients undergoing these operations as primary procedures for stress incontinence is in the range of 70% to 90% (88,101,102,103,104).**

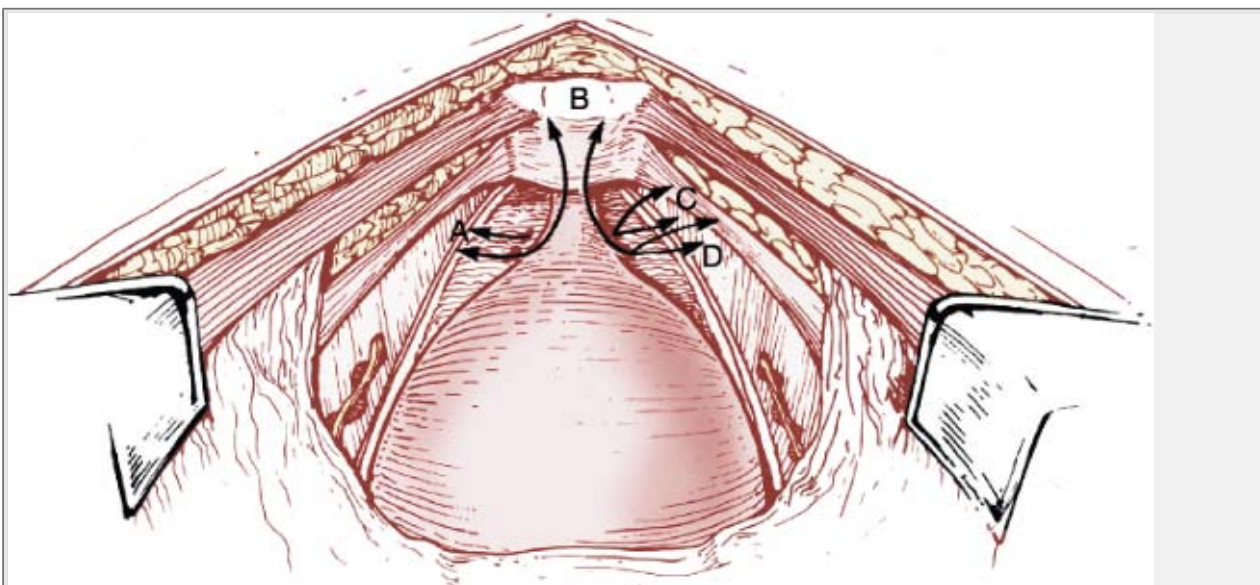


Figure 23.10 Points of reattachment of the endopelvic fascia during retropubic bladder neck suspensions. **A:** Arcus tendineus fascia pelvis (for paravaginal repair). **B:** Periosteum of pubic symphysis (for Marshall–Marchetti–Krantz procedure). **C:** Iliopectineal, or Cooper's, ligament (for Burch colposuspension). **D:** Obturator internus fascia (also used for paravaginal, or obturator shelf, repair).

In 1991, Vancaille introduced the laparoscopic colposuspension to meet the growing demand for a minimally invasive surgical approach to stress urinary incontinence. In a summary of randomized comparisons between laparoscopic and open colposuspensions, the Cochrane Incontinence Group concluded that laparoscopic colposuspension may have short-term benefits, such as quicker recovery, but may have more complications and be more costly because it takes longer to perform than other surgical procedures for stress urinary incontinence. The long-term success of laparoscopic colposuspension is unclear, but there is limited evidence to suggest the results are less favorable than with open colposuspension, although this may reflect a learning effect and is unreliable in isolation (105).

Traditional Pubovaginal Sling

Sling operations have traditionally been performed using a combined vaginal and abdominal approach (Fig. 23.11). The anterior vagina is opened, the space of Retzius is dissected on each side of the bladder neck, and a sling is passed around the bladder neck and urethra and then attached to the anterior rectus fascia or some other structure to cradle the urethra in a supporting hammock. This both supports the urethra and allows it to be compressed during periods of increased intra-abdominal pressure (106,107,108,109,110,111,112,113,114,115,116). The sling can be made of organic or inorganic materials. Organic materials can be autologous tissues harvested from the patient (e.g., fascia lata, rectus fascia, tendon, round ligament, rectus muscle, vagina), processed allografts from human donors (e.g., fascia lata, dermis), or heterologous tissues harvested from another species and processed for surgical use (e.g., ox dura mater, porcine dermis). Synthetic materials (e.g., Silastic, Gore-Tex, Marlex) are popular because of their consistent strength and availability, but historically these substances have been plagued by problems with erosion and infection when used around the urethra (75,117,118).

Minimally Invasive Sling

In the 1990s, various orthopedic bone anchors were marketed to implant into the pubic bone to suspend the urethra with sutures or slings. Despite a lack of medical evidence to support either the bone anchor or the allograft use, bone anchor systems became the quick and minimally invasive method to suspend allograft slings (119). Although bone anchors have not been shown to be superior to standard fixation techniques, their use has led to increased complications in several series.

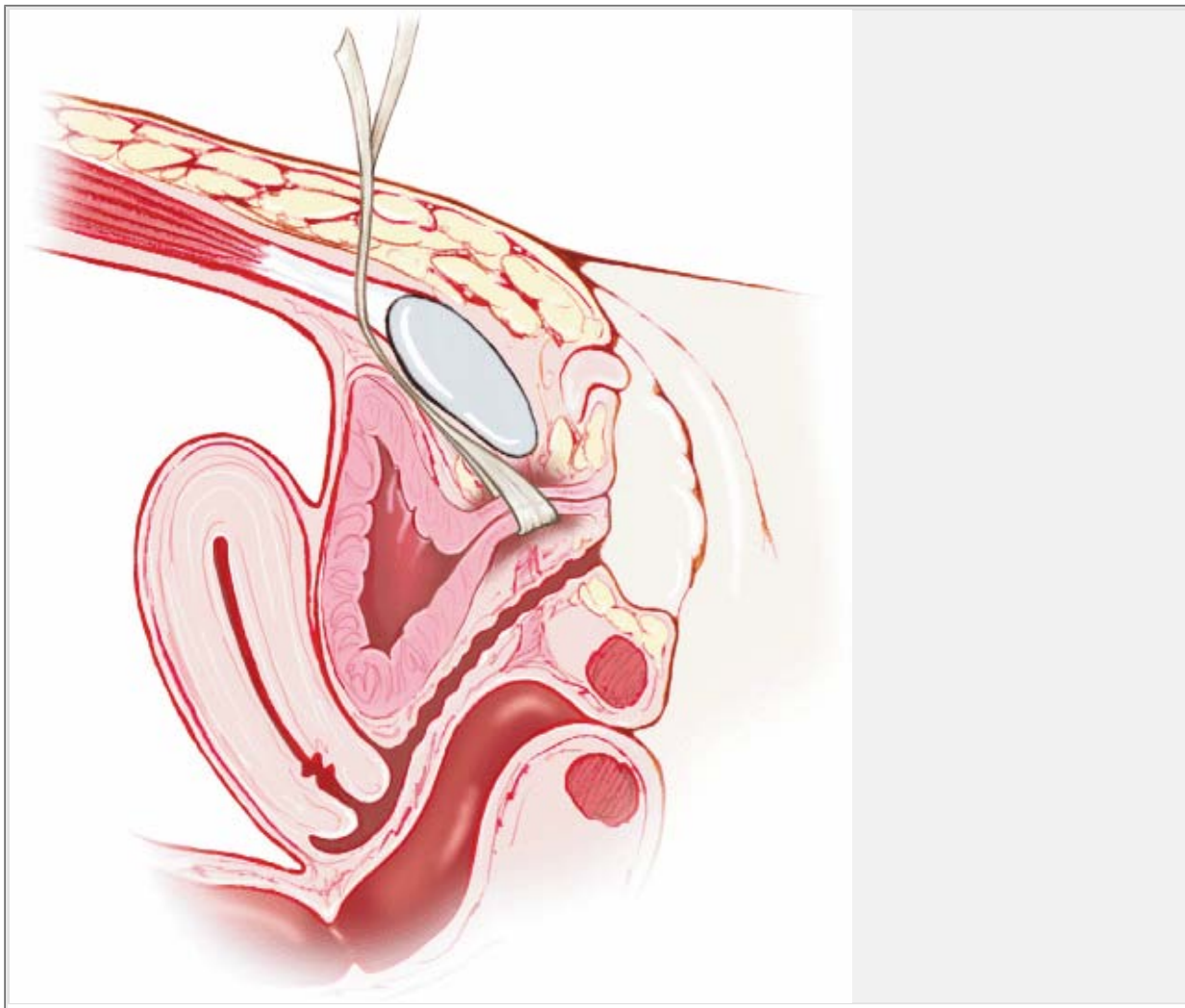


Figure 23.11 A completed traditional suburethral sling procedure with the fascia located at the bladder neck with the ends of the sling tied to or above the rectus fascia. The classic procedure uses autologous fascia; however, some surgeons use allograft or xenograft tissue performed in a similar fashion. Redrawn from original by Jasmine Tan.

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In 1996, Falconer et al. described the tension-free vaginal tape (TVT) for correcting stress urinary incontinence (120). In this technique, polypropylene mesh is placed under the midurethra with minimal tension (Fig. 23.12, A and B). To perform this operation, a small midurethral incision is made in the vaginal epithelium mucosa. A 40 × 1-cm mesh tape covered by a plastic sheath and attached to two 5-mm curved trocars is passed lateral to the urethra and through the endopelvic fascia into the retropubic space. The trocar is then passed along the back of the pubic bone, through the rectus fascia, into two small suprapubic skin incisions. The tension on the tape is adjusted, the sheath is removed, and the remaining tape is cut off at the level of the skin. This technique has the advantage of being performed quickly using limited anesthesia (fewer than 30 minutes in experienced hands). The procedure requires the use of a catheter guide to deviate the urethra and cystoscopy to ensure that bladder or urethral perforations are recognized immediately because the trocar is passed blindly.

Since its introduction, there have been scores of articles published suggesting that TVT is generally effective and safe and similar in effectiveness to colposuspension. Larger, multicenter trials provide the most realistic look at outcomes of a surgical procedure by many surgeons with varying experience on a wide array of patients. **A report of the 2-year follow-up of 344 women with urodynamic stress incontinence enrolled from 14 centers in a multicenter randomized clinical trial compared TVT and open Burch colposuspension. The objective cure rates (defined as a negative 1-hour pad test) ranged from 63% to 85% for the TVT procedure and 51% to 87% for open colposuspension, depending on how missing data were handled, leading the authors to conclude that "TVT may be better, worse, or the same as open colposuspension in the**

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cure of stress incontinence." Subjectively, only 43% of women in the TVT group and 37% of women in the open colposuspension group reported cure of their stress leakage. Women undergoing the TVT were more likely to have a cystocele after surgery, whereas those undergoing the Burch colposuspension were more likely to have apical prolapse. Two years after the index procedure, seven women (4.8%) in the Burch colposuspension group underwent surgery for pelvic organ prolapse, compared with no women in the TVT group. There was no difference in the number of women that underwent repeat surgery for stress incontinence (1.8% in the TVT group and 3.4% in the Burch group). Women who underwent TVT were less likely to have voiding disorders requiring intermittent self-catheterization than those who underwent colposuspension (0% vs. 2.7%) (121).

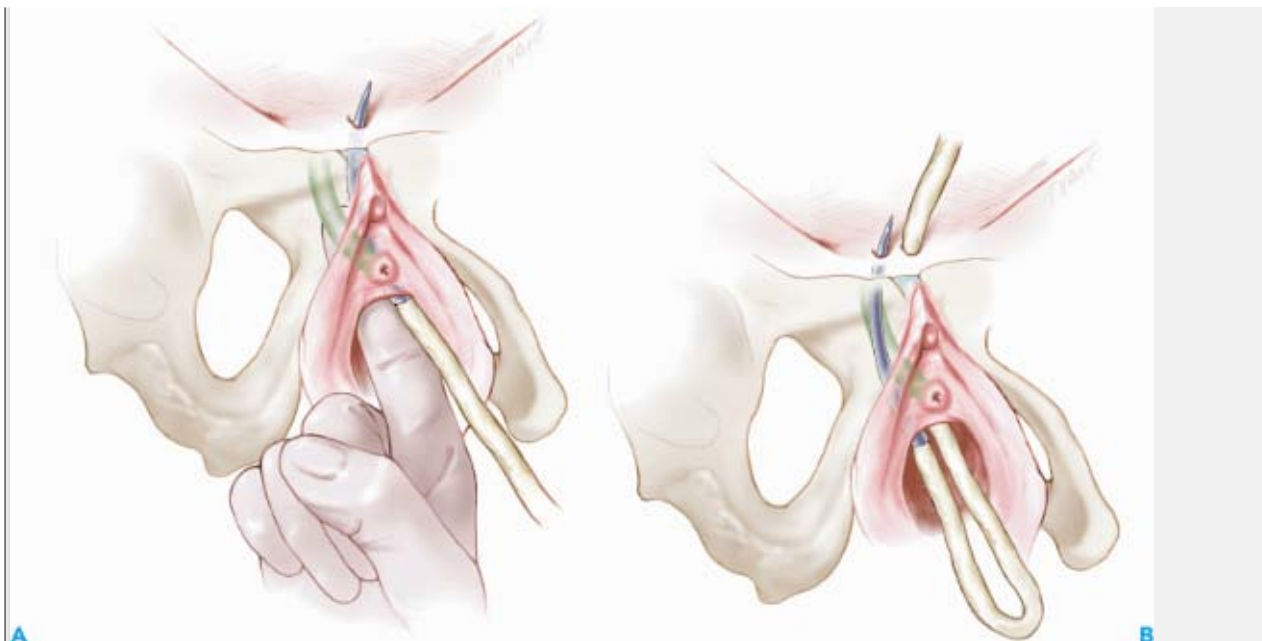


Figure 23.12 Midurethral synthetic slings involve the use of large pore, monofilament polypropylene mesh placed after minimal dissection at the midurethra followed by placement of a trocar through the retropubic route. Some surgeons prefer placing the trocar by a suprapubic route beginning with a small abdominal incision. A: The trocar is guided into the previously performed midurethral incision with care to place the trocar against the pubic bone to avoid entry into the peritoneal cavity. The trocar handle has been removed in this view after perforation through the abdominal incision. B: The synthetic sling should rest in the midurethra location and is brought through two stab incisions above the pubic symphysis. Redrawn from original by Jasmine Tan.

Over the past 5 years, numerous modifications of the TVT have been proposed and marketed. Such devices generally circumvent the stringent regulatory control provided by the U.S. FDA by gaining approval through a Premarket Notification 510(k). This mechanism is a submission to the FDA demonstrating that a new device is substantially equivalent either to a legally marketed or "predicate" device introduced before 1976 in the United States or to one approved by the FDA through the 510(k) process itself. Substantial equivalence means the new device has the same intended use as the "predicate" device *and* has the same technological characteristics *or* different technological characteristics, but it is as safe and effective as the "predicate" device. **Surgeons should be aware that most new devices for urinary incontinence are not tested in clinical trials before they are marketed.**

One modification gaining favor is the transobturator tape procedure (also known as a TOT, transobturator suburethral tape, subfascial hammock, and TOMUS—transobturator

midurethral sling). This modification was designed to reduce complications associated with retropubic needle passage. Inserting the trocar through the obturator space theoretically lessens the risk of bladder, bowel, or vascular injury because the procedure involves passing the polypropylene midurethral sling through the obturator membrane along its ischioanal fossa path, bypassing the pelvic cavity altogether.

Currently, data on this technique are limited. One report showed no bladder perforations in the first 71 transobturator tape procedures performed and, in 68 patients examined 6 to 12 weeks postoperatively, 64 were cured and 2 improved (122). Another report indicated a 90.6% cure rate in 32 patients who were followed for a minimum of 1 year. Five patients had voiding disorders suggestive of bladder outflow obstruction, but only one required self-catheterization for 1 month. No problems with urethral erosion, residual pain, or

functional impairment were reported (123). In a multicenter trial, 183 women from seven sites underwent a transobturator tape procedure for stress and mixed urinary incontinence. At one year follow up 80.5% patients were cured. (defined as absence of subjective report of stress urine leakage and negative cough stress test). Perioperative complications included one bladder perforation, two urethral perforations, and one lateral vaginal perforation. Tape erosion necessitating removal occurred in five cases (three vaginal and two urethral). Cystoscopy was not routinely performed (124).

Bulking Agents

Injectable (so-called bulking) agents are less invasive than surgery, and although they are less likely to result in cure than surgery, they relieve symptoms in many women. In the United States, glutaraldehyde cross-linked bovine collagen (*Contigen*) and carbon beads (*Durasphere*) are approved for use to treat stress urinary incontinence and can be injected either peri- or transurethrally. Injecting a material around the periurethral tissues facilitates coaptation of the urethra under conditions of increased intra-abdominal pressure (125,126,127,128,129,130). In a 15-article review, the short-term cure or improvement rate was 75% (131). *Contigen* can be passed easily through small-bore needles under local anesthesia but requires preoperative skin testing to check for possible allergic reactions (3%). *Durasphere* is nonantigenic (thus no skin testing is required) and does not migrate. As compared with collagen, *Durasphere* appears to have similar reduction in leakage episodes and is more likely to require only a single injection (132). This bulking agent does require a larger-gauge needle for injection and is somewhat more difficult to inject than collagen. These techniques may require several injections to achieve continence, and the long-term success of these operations remains poorly studied. It is known, however, that success declines with time, and patients often need additional procedures every 1 to 2 years. New, longer-acting agents are in development and potentially will decrease the interval between injections.

Complications

In choosing surgical management, surgeons must weigh the chance of cure against the chance of severe complications. In the aforementioned randomized trial comparing TVT and Burch, **women undergoing TVT were more likely to experience a bladder perforation than those undergoing the Burch procedure (9% versus 2%, respectively) but less likely to have a fever (1% versus 5%) or prolonged catheterization more than 29 days (3% versus 13%)** (133). Less common complications require a large sample size to detect differences. In the randomized trial, 2% of women in the TVT group had a retropubic hematoma and 1% a vascular injury, compared with no women in the Burch group. Given the small numbers, it is not clear whether the rate of vascular injuries differs. In a report to the FDA in which worldwide safety data from more than 500,000 procedures were summarized, there were seven deaths reported after TVT, six associated with bowel perforation and one from vascular injury. No such data are available for Burch urethropexy.

In a nationwide analysis of 367 complications associated with 1,455 TVT procedures performed in Finland, there was a 1.9% rate (95% CI, 1.2–2.7) of blood loss over 200 mL, a 1.9% rate (95% CI, 1.2–2.7) of retropubic hematoma, a 0.5% rate (95% CI, 0.2–1.0) of

hematoma outside the retropubic area, a 0.1% rate (95% CI, 0.0–0.4) of injury to the epigastric vessel, a 0.1% rate (95% CI, 0.0–0.4) of injury to the obturator nerve, and a 3.8% rate (95% CI, 2.9–5.0) of bladder perforation (134).

Erosion is unique to surgeries in which a graft is placed, and the rate depends largely on the type of graft used. Rates from one type of material cannot be extrapolated to another. Tension-free vaginal tape is associated with a low rate of graft erosion, compared with a much higher rate of erosion with certain synthetics used for pubovaginal slings in the past. In the randomized trial comparing Burch and TVT described previously, of the 170 women who underwent a TVT procedure, one woman had a graft erosion in the first 6 months, and two others had graft erosion or extrusion between 6 and 24 months postoperatively (121).

The most common adverse events (generally 5%–10% rate for each) after all surgeries for stress urinary incontinence include urinary tract infection, failure to cure, new onset detrusor overactivity, voiding dysfunction, genital prolapse, and bladder perforation. When new onset detrusor overactivity occurs after surgery for incontinence, cystoscopy should be considered to rule out a foreign body in the bladder (Fig. 23.13). Less common events (generally 2%–5% for each) include excessive blood loss, wound infection, pain, nerve injury, or incisional hernia. Events such as sinus tracts and fistulae are rare. Erosion rates depend on the material implanted and, as noted previously, are rare for the newer midurethral slings. In addition, medical events, such as thromboembolic, cardiac, or pulmonary events, are rare.

Surgical Treatment for Detrusor Overactivity

Neuromodulation

Even with the development of newer anticholinergic medications with fewer side effects, there continues to be a select group of patients with overactive bladders who remain refractory to standard medical and behavioral treatment. Surgical treatment of this condition has traditionally involved substantial morbidity and major urinary denervation, reconstruction, or both to achieve therapeutic benefits. The development of implantable sacral nerve root stimulators led to FDA approval of sacral root neuromodulation in patients with refractory urinary urgency and frequency, urge incontinence, and voiding dysfunction. This therapy offers patients with severe symptoms an alternative to urinary augmentation or diversion. **Sacral nerve stimulation therapy** is performed in two phases. In the first phase, a **percutaneous nerve evaluation test** is performed to determine which patients respond to this type of therapy. **Those who respond are then implanted with a permanent electrode lead adjacent to the third sacral nerve root connected to a pulse generator.**

A multicenter prospective study demonstrated that 63% of test patients responded to the initial procedure. After implantation, 47% of patients became completely dry, and 77% were successful in eliminating "heavy" leakage episodes. **Despite substantial success in nearly 80% of patients who received implants, 30% of patients required further surgical revision because of pain or other complications at the generator or implant site.** No permanent injuries or nerve damage was reported in the initial trials (135,136).

In a group of 96 patients with implants (who responded favorably during the test stimulation period), reductions in urge incontinence episodes and severity were still seen at an average of 31 months after implantation. The device was removed in 11 of the 96 patients because of lack of efficacy, pain, or bowel dysfunction. There were no permanent injuries (137). The technique for this procedure has evolved over the last several years to include the location of a generation implant site on the back and the performance of the procedure in two stages with initial percutaneous implantation of a quadpolar instead of a unipolar stimulator. These modifications may improve success rates and decrease the morbidity associated with these procedures.

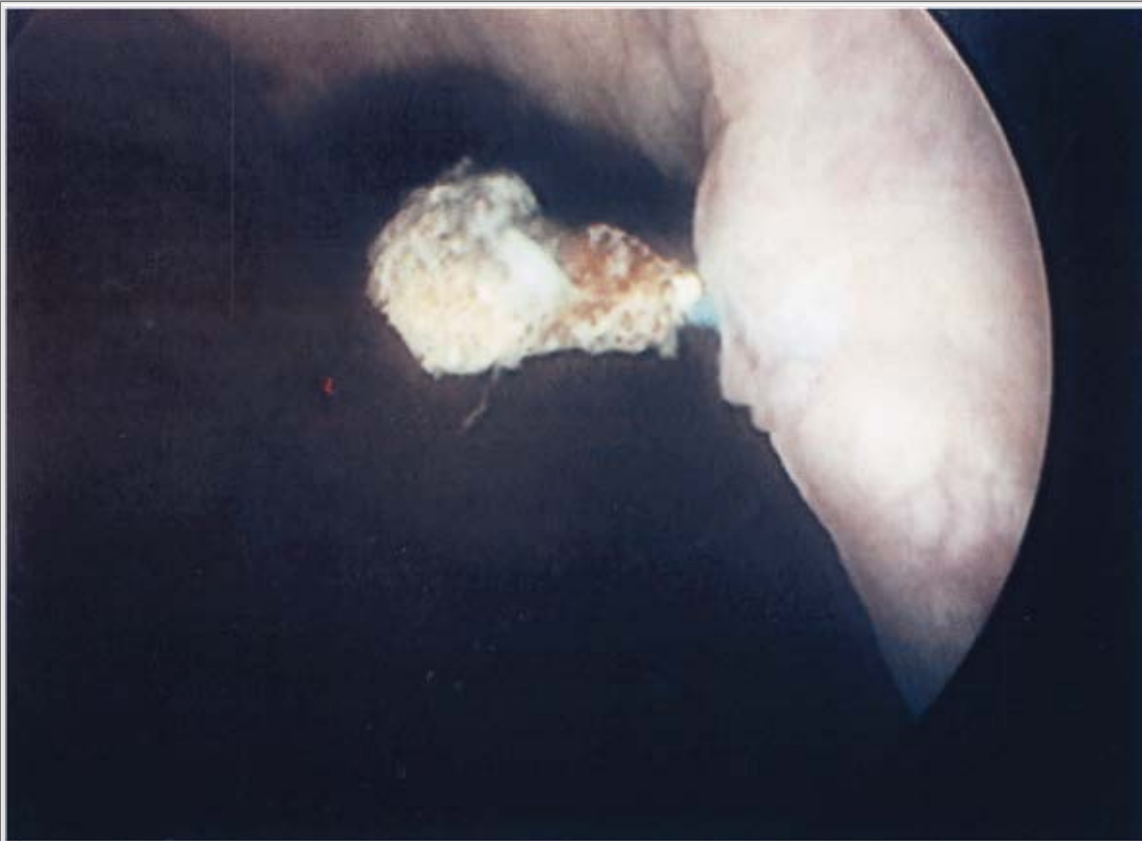


Figure 23.13 Cystoscopic view of encrusted suture penetrating bladder wall following sling urethropexy.

Botox Injections

Botulinum toxin A (BtxA), a neurotoxin produced by the anaerobic bacteria *Clostridium botulinum*, acts on peripheral cholinergic nerve endings to inhibit calcium-mediated release of acetylcholine vesicles at the presynaptic neuromuscular junctions. Researchers describing the use of BtxA for detrusor overactivity in spinal cord injury patients reported that 17 of 19 were completely dry 6 weeks after treatment (138). In a report from a multicenter study, a 73% continence rate occurred in 180 patients with neurogenic detrusor overactivity incontinence who underwent cystoscopic Botox injections (139).

The procedure is done via cystoscopy and involves injecting 15 to 30 different detrusor muscle sites under direct visualization, sparing the bladder trigone and ureteral orifices. The off-label use of Botox A cystoscopic detrusor injections to treat refractory detrusor overactivity (in women with and without neurologic impairment) is gaining popularity. Clinical trials assessing effectiveness and side effects are ongoing.

Augmentation Cystoplasty and Urinary Diversion

Surgery to replace the function of a diseased bladder has been done for more than a century and Urinary Diversion and, over the past several decades, gained some popularity in treating people with intractable detrusor overactivity not responsive to any other form of management. **These surgical options include (i) conduit diversion (creation of various intestinal conduits to the skin) or continent diversion (which includes a rectal reservoir or continent cutaneous diversion), (ii) bladder reconstruction, or**

(iii) replacement of the bladder with various intestinal segments. These techniques, both historical and current, are beyond the scope of this chapter; the interested reader is referred to a review by Greenwell et al. (140). In a Cochrane review, the reviewers found only two randomized trials that were of sufficient quality to include and concluded that there were no major differences in outcomes between the techniques and that higher quality research was needed (141). With the advent of sacral neuromodulation, these procedures are done much less often to treat women with detrusor overactivity.

Surgical Treatment of Fistulae

A wide variety of techniques are available for fistula repair (142,143). Traditionally, fistula repair has been performed after a waiting period to allow the resolution of inflammation and formation of scar tissue. This is particularly important in the case of obstetric fistulas, in which the extent of the vascular injury to the soft tissues of the pelvis may not be apparent for many weeks. However, there has been a recent trend toward early closure of small gynecologic fistulas (144). The keys to closure of a vesicovaginal fistula include wide mobilization of tissue planes so that the fistula edges can be approximated without any tension, close approximation of tissue edges, closure of the fistula in several layers, and meticulous attention to postoperative bladder drainage for 10 to 14 days. The closure of large fistulas will be enhanced by the use of tissue grafts (e.g., Martius labial fat-pad grafts, gracilis muscle flaps) that provide an additional blood supply to nourish an area that has sustained vascular injury. The Latzko procedure used to close a vesicovaginal fistula is shown in Figure 23.14.

Cystoscopy

Scientific evidence does not support routine cystoscopy in women with stress urinary incontinence in the absence of other pathologies (145). Cystoscopy cannot be used to predict intrinsic sphincteric deficiency, stress incontinence, or detrusor overactivity. Cystoscopy can be considered in the following circumstances: (i) in women with urge incontinence to rule out other disorders, especially in women with microscopic hematuria, (ii) in the evaluation of vesicovaginal fistulae, and (iii) intraoperatively to evaluate possible ureteral or vesical injury.

Urologists often use flexible cystoscopy in men; however, women tolerate a rigid cystoscope well, given their short urethras and absence of prostate glands. The view afforded by a rigid cystoscope is clearer than that obtained with a flexible scope, and less technical skill is required to view the entire bladder using a rigid scope. **Cystoscopes are available with several viewing angles: 0° (straight), 30° (forward-oblique), 70° (lateral), and 120° (retroview).** The last scope is rarely used in women. Zero-degree lenses are essential for viewing the urethra, whereas a 30° lens provides the best view of the bladder base and posterior wall, and the 70° lens generally provides the best view of the anterior and lateral walls. For diagnostic cystoscopy, sterile water is an ideal medium because it is readily available and inexpensive.

To evaluate the urethra, the cystoscope should be advanced with distension medium flowing, keeping the center of the urethral lumen in the center of the visual field. The mucosa is normally pink and smooth and the urethral folds close.

To examine the bladder, the cystoscope should be inserted into the bladder with both the light cord and the camera cord oriented toward the floor. When using a 70° lens, this will show the bladder dome, which is easily identified by an air bubble anteriorly. The remainder of the bladder is then systematically examined by making a series of sweeps, slowly rotating

the cystoscope between the dome and urethrovesical junction. To view the trigone, the light cord should be oriented toward the ceiling (keeping the camera cord toward the floor). The scope is pulled back until it is almost in the urethra, and the base of the bladder is then viewed. Because the trigone is a zone of metaplasia, it generally looks different from the rest of the urothelium (Fig. 23.15).

Vaginal and abdominal hysterectomies are associated with a 0.02% to 0.85% incidence of ureteral injury (146). However, the injury rate increases in reconstructive pelvic surgeries, reaching as high as 11% after uterosacral ligament suspension (147). In a study of 46 women that underwent proximal uterosacral ligament vaginal vault suspension, three of the five women with cystoscopic evidence of obstruction were treated

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by simply removing and replacing the sutures. This finding emphasizes the importance of confirming ureteral integrity at surgery.

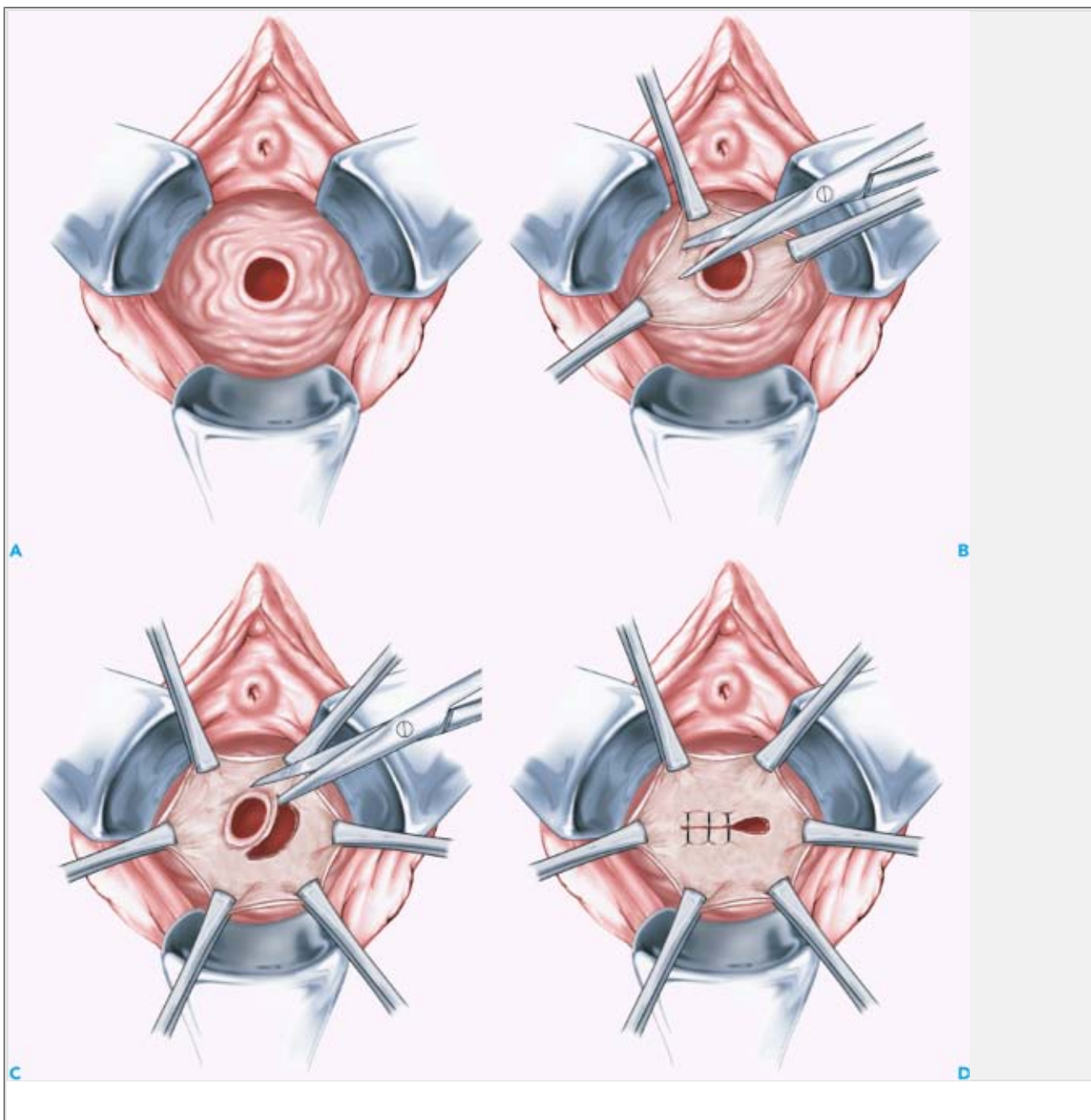


Figure 23.14 Repair of apical vesicovaginal fistula. A: The fistula at the vaginal apex is exposed with adequate retraction. A pediatric foley B: The vaginal epithelium is dissected from the fistula to mobilize the tissue to allow for tension-free closure. In the classic Latzko procedure, the vaginal epithelium 2 cm around the opening of the fistula is removed. C: The fistula tract may either be completely excised, or in the Latzko procedure, the fistula edge may freshened up slightly but is not excised. D: Interrupted absorbable sutures are placed in an extramucosal location in an interrupted fashion. An additional layer of interrupted sutures is often placed to invert the initial suture line. The vaginal epithelium is then closed over the repair. In the classic Latzko procedure, the initial layer involves closure of the vagina over the fistula tract, then two additional layers with the vaginal epithelium result in an apical colpocleisis. Redrawn from original by Jasmine Tan.

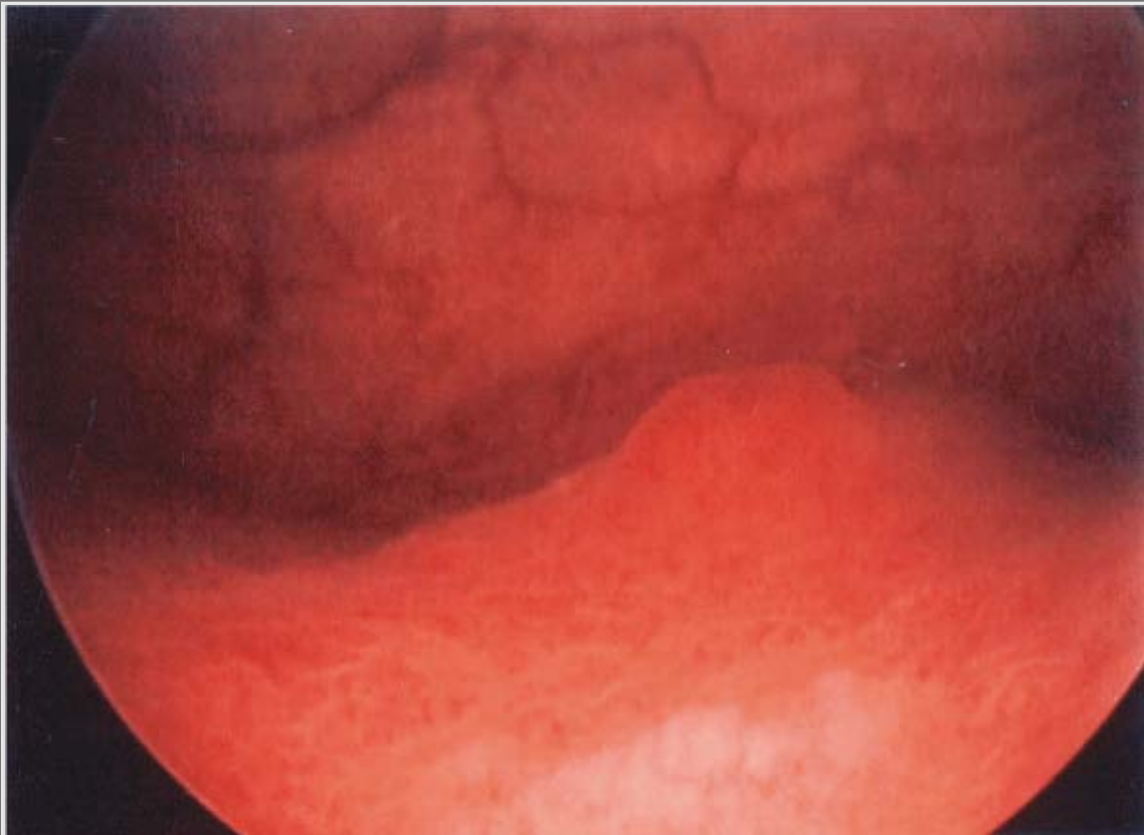


Figure 23.15 Cystoscopic view of normal-appearing trigone with left ureteral orifice visible.

Administering indigo carmine dye intravenously 5 minutes before cystoscopy aids in the assessment of ureteral patency. Quick efflux of stained urine should be seen bilaterally. Sluggish efflux should prompt further investigation. However, pre-existing ureteral obstruction may also be responsible for lack of flow. In 157 women who underwent complex urogynecologic procedures, 5 (3.2%) cases of unsuspected ureteral obstruction were identified with intraoperative cystoscopy (148). One was due to ureteral ligation, and the remaining four represented chronic ureteral obstruction resulting from pelvic organ prolapse (two cases), ureteropelvic junction obstruction (one case), and ureterovesical junction stenosis after prior transurethral resection of bladder cancer (one case).

Voiding Dysfunction and Bladder Pain Syndromes

Voiding Dysfunction

Women are afflicted less commonly than men with voiding difficulties, but these disorders do occur in women and can be defined as emptying dysfunction resulting from relaxation of the pelvic floor musculature or failure of the detrusor muscle to contract appropriately. **True outflow obstruction (defined as a detrusor pressure of more than 50 cm H₂O in association with a urine flow rate of less than 15 mL/sec) is rare in women and, when seen, is usually found in those who have undergone obstructive bladder neck surgery for stress incontinence (149,150). For normal voiding to occur, the pelvic floor and urethral sphincter must relax, which should occur in conjunction with a coordinated contraction of the detrusor muscle that leads to complete bladder emptying.** The bladder may also be emptied by other mechanisms, such as by abdominal straining in the absence of a detrusor contraction, or simply by relaxation of the pelvic floor. Complete bladder emptying is not the same as normal voiding. Some women may empty their bladders

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completely but only by expending great effort over several minutes. In such cases, voiding is clearly abnormal, even though the bladder is empty when voiding ceases. In the worst cases, voiding is both difficult and incomplete.

Causes

Neurologic diseases, such as multiple sclerosis, may cause voiding difficulty as a result of *detrusor-sphincter dyssynergia* (151,152), in which the urethral sphincter contracts at the same time as the detrusor. Great effort is required to overcome urethral resistance; the patient voids with an interrupted stop-and-start stream and usually has a significant amount of residual urine.

Other causes of voiding difficulty include medications (such as antihistamines and anticholinergic agents), infections (in particular, herpes simplex virus and urinary tract infections), obstruction (following bladder neck surgery, or in women with advanced pelvic organ prolapse), overdistension, severe constipation (particularly in elderly), and, rarely, psychogenic factors. Fowler's syndrome refers to unexplained urinary retention occurring as an isolated phenomenon (153). Generally such women are between 20 and 35 years of age. Commonly the first retention episode will be triggered by an event such as surgery or childbirth. Retention rarely resolves but is not associated with the development of other disorders.

Evaluation

Evaluation of a woman with voiding difficulty begins with a careful physical examination. **Advanced pelvic organ prolapse may contribute to urinary retention, but it is unlikely that prolapse above the level of the vaginal introitus will be the sole cause of retention.** When in doubt, the woman can wear a pessary for a week to see whether elevating the prolapse reduces the voiding difficulty. Occasionally pelvic masses—in particular, low anterior myomas—may cause urinary retention. Abnormal findings detected during neurologic examination of the perineum and lower extremities may suggest the need to focus on the spine. Urodynamics evaluation will help determine whether the woman has an obstruction (manifested by high detrusor pressures during voiding or by no urethral relaxation during voiding) or whether the detrusor muscle is not contracting. The latter is not necessarily indicative of a neurogenic disorder in women, as a large minority of normal healthy women void by urethral and pelvic floor muscle relaxation alone, with no

detrusor contraction. Cystourethroscopy may reveal an obstructing lesion, such as a polyp, tumor, ureterocele, or ball-valve stone. Usually, the evaluation reveals no obvious source, and treatment can commence.

Treatment

The mainstay in the treatment of voiding difficulty is clean, intermittent self-catheterization (154). The most important protection against urinary tract infection is frequent and complete bladder emptying rather than avoiding the introduction of a foreign body into the bladder. Self-catheterization allows the patient to accomplish this task using a small (14-Fr.) plastic catheter that she inserts through the urethra into the bladder, draining its contents. The catheter is then removed, washed with soap and water, dried, and stored in a clean, dry place. Elaborate sterile procedures are not necessary. Bacteria are introduced into the bladder in this process, and the urine of women after self-catheterization regimens will always be colonized with bacteria; however, this condition should not be treated unless symptomatic infection occurs.

In addition to decreasing urinary urgency and incontinence caused by detrusor overactivity, neuromodulation of the sacral nerve roots also may help women with nonobstructive urinary retention (136). In a trial of 177 patients with idiopathic urinary retention, those who had greater than 50% improvement in baseline voiding symptoms during a test stimulation period qualified for surgical implantation of InterStim. Of these, 37 were randomly assigned to early implantation, whereas 31 in the control group delayed implantation for

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6 months. Improved voiding occurred in 83% of the implant group compared with 9% of the control group at 6 months (155). Although this technology requires a major surgical procedure, many women favor this therapy over lifelong self-catheterization.

Mild sedatives are sometimes helpful in this process, as are α -blockers (e.g., *prazosin*, *phenoxybenzamine*), which reduce urethral tone. For patients who are unable to generate a detrusor contraction, attempts have been made to enhance detrusor contractility using a cholinergic agonist such as *bethanechol chloride*. Although cholinergic medications are successful in making strips of bladder muscle contract in a laboratory, there is little evidence that such drugs are helpful clinically (156).

Bladder Pain Syndromes

Most patients with disorders of bladder sensation experience pain rather than lack of bladder sensation. As with the treatment of most chronic pain disorders, the cause of most painful bladder conditions is unknown, and the therapies currently used are only partially successful. As a result, disorders of bladder sensation are among the most frustrating urogynecologic conditions to manage.

Terminology and Prevalence

Painful bladder syndrome, often termed *interstitial cystitis*, is a poorly defined heterogeneous syndrome, and diagnostic criteria are changing continuously. **The latest International Continence Society standardization report recommends adapting the term *painful bladder syndrome*, rather than *interstitial cystitis* and defines painful bladder syndrome as the "suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology" (7). Urgency and pain are the defining characteristics of painful bladder syndrome** (157). Several

factors have inhibited advances in the understanding of interstitial cystitis, including the lack of specific diagnostic criteria, the lack of specific histopathologic changes, the unpredictable fluctuation in symptoms, and the marked variability among patients in terms of symptoms, objective findings, and treatment responses (158).

The National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) developed a research definition for interstitial cystitis that requires objective findings of glomerulations or a classic Hunner's ulcer during hydrodistention of the bladder and subjective symptoms of bladder pain or urinary urgency in the absence of other urogenital pathology (159). Strict application of NIDDK criteria in one study would have misdiagnosed more than 60% of patients thought to definitely or possibly have interstitial cystitis (160). Many clinicians have challenged the clinical utility of the NIDDK research criteria, and most conceptualize interstitial cystitis as the end point on the spectrum of painful bladder disorders (162).

The prevalence of painful bladder syndrome varies widely depending on the diagnostic criteria utilized. When mild and moderately severe cases are considered, the syndrome is not rare (162). Estimates of prevalence in the United States range from 52 per 100,000 women in the population-based Nurses Health Study to as high as 1 in 4.5 women "with accurate diagnostic records" (163,164). The prevalence appears to be 6 to 15 times more common among women than men (163,165). The identification of risk factors for painful bladder syndrome is particularly challenging because of the typically long delay in diagnosis (163). The recently completed Interstitial Cystitis Database study confirms many of the previous epidemiologic observations: Affected individuals are predominately female (92%), white (91%), and report an average age of symptom onset of 32.2 years (158,163).

Diagnosis

A careful history should be obtained, along with a sterile urine specimen for analysis and culture. Many women treated repetitively for chronic cystitis have taken multiple courses

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of antibiotics on the basis of symptoms without ever having the presence of an infection confirmed by cultures. Detrusor overactivity may be the cause of frequency, urgency, and urge incontinence but is not usually a factor in dysuria or painful urination. **Women older than 50 years (particularly those who smoke or are exposed to chemicals at work) are at risk for bladder cancer, and this possibility must be considered, especially if hematuria is present.** Urinary cytologic assessment is sometimes helpful in detecting early tumors of the urinary tract, and cystoscopy and intravenous urography are mandatory in the evaluation of patients with hematuria.

Other possible causes for painful voiding must be considered in the differential diagnosis, including urethral diverticula; vulvar disease; endometriosis; chemical irritation from soaps, bubble bath, or feminine hygiene products; urinary stones; urogenital atrophy from estrogen deprivation; and sexually transmitted disease (165).

The diagnosis of interstitial cystitis is largely one of exclusion. The ideal diagnostic test for interstitial cystitis has not been determined, and there are myriad proposed tests.

Treatment

Typically, the evaluation of painful bladder syndrome results in no definitive diagnosis, and management focuses on the treatment of symptoms.

Frequency-urgency syndromes should be managed with a careful voiding regimen

(similar to that used in the treatment of detrusor overactivity) and local care.

The use of urinary tract analgesics such as *Urised* may be helpful in reducing urethral irritation. *Urised* is a polypharmaceutical agent containing a mixture of *methenamine*, *methylene blue*, *phenyl salicylate*, *benzoic acid*, *atropine sulfate*, and *hyoscyamine* that has a soothing effect on many irritative urethral symptoms.

There is no scientific evidence linking diet to painful bladder syndrome, but many doctors and patients find that alcohol, tomatoes, spices, chocolate, caffeinated and citrus beverages, and high-acid foods may contribute to bladder irritation and inflammation. Some patients also note that their symptoms worsen after eating or drinking products containing artificial sweeteners. Patients may try eliminating various items from their diet and reintroducing them one at a time to determine which, if any, affect their symptoms. Instruction in the basics of vulvar and perineal hygiene is important (thorough drying; avoidance of most body powders, perfumes, or colored irritating soaps; avoidance of tight-fitting undergarments) to avoid other factors that may contribute to painful voiding.

Hydrodistention of the bladder (usually under anesthesia) has been recommended as a treatment option and can result in clinical improvement in some patients. Some patients benefit from the instillation of 50 mL of a 50% solution of *dimethylsulfoxide* (DMSO) for 20 to 30 minutes every other week for four or five sessions.

Pentosan polysulfate (*Elmiron*) is an FDA-approved oral agent with heparinlike activity that attempts to replace the glycoaminoglycan sulfate layer that is believed deficient in these patients. In clinical trials, the drug improved symptoms in 38% of patients treated. The FDA-recommended oral dosage of *Elmiron* is 100 mg, three times a day. Patients may not feel relief from pain for the first 2 to 4 months, and it may take up to 6 months for a decrease in urinary frequency to occur.

Because it has been theorized that bladder pain may result from increased histamine release, some patients benefit from medications that block these inflammatory mediators, such as *diphenhydramine hydrochloride*, 25 to 50 mg orally three times per day, in combination with 300 mg of *cimetidine* three times per day. Tricyclic antidepressants help some women by modulating sensory nerve pain.

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Transcutaneous electrical nerve stimulation (TENS), through wires placed on the lower back or just above the symphysis, may help some women, though the mechanism of action is unclear. Ongoing preliminary research suggests that some women with severe bladder pain syndrome may find relief following sacral neuromodulation (*InterStim*) or acupuncture.

In 1998, NIDDK initiated the Interstitial Cystitis Clinical Trials Group, a multicenter group charged with developing and testing new treatment strategies for patients with this disorder. It is hoped that research such as this will ease the great suffering by women with painful bladder syndrome and improve their quality of life.

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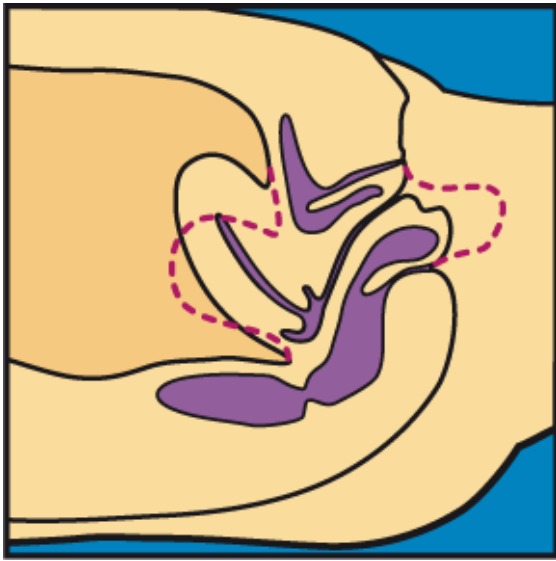
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24

Pelvic Organ Prolapse

Holly E. Richter

R. Edward Varner



- **With the aging of the population, pelvic organ prolapse is an increasingly common condition seen in women.**
- **Causes of pelvic organ prolapse are multifactorial and result in weakening of the pelvic support connective tissue and muscles as well as nerve damage.**
- **Patients may be asymptomatic or have significant symptoms such as those relating to the lower urinary tract, pelvic pain, defecatory problems, fecal incontinence, back pain, and dyspareunia.**
- **Physical examination includes thoughtful attention to all parts of the vagina, including the anterior, apical, and posterior compartments, levator muscle, and anal sphincter complex.**
- **Nonsurgical treatment options include pelvic floor muscle training and the use of intravaginal devices.**
-

Surgical treatment involves an individualized, multicompartamental approach consistent with the patient's previous treatment attempts, activity level, and health status.

- **Studies are needed to determine the characteristics of those patients who would benefit long-term from vaginal versus abdominal approaches to the surgical repair of pelvic organ prolapse.**

Pelvic organ prolapse (POP) is a bulge or protrusion of pelvic organs and their associated vaginal segments into or through the vagina (1). It is a common and costly affliction of older women (2,3). **It has been estimated that over the next 30 years, the demand for treatment of POP will increase 45%, commensurate with an increase in the population of women older than 50 years of age (4,5).** As this problem grows in significance, it becomes increasingly important to work toward an understanding of the pathophysiology and risk factors associated with pelvic organ prolapse to try to prevent its occurrence. Furthermore, continued efforts are needed to understand factors that result in long-lasting, robust repair of pelvic organ prolapse for those patients undergoing surgical management.

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Despite extensive anecdotal experience, the optimal surgical approach to apical and other compartment prolapse remains elusive (6).

In the United States, 11% of women up to the age of 80 years have surgery for pelvic organ prolapse or urinary incontinence, and nearly one third of procedures are repeat surgery (3). Data from the Women's Health Initiative revealed anterior pelvic organ prolapse in 34.3%, posterior wall prolapse in 18.6%, and uterine prolapse in 14.3% of women in the study (7). In this study, a significant risk factor associated with prolapse was vaginal delivery. After adjusting for age, ethnicity, and body mass index, women with at least one vaginal delivery were twice as likely as nulliparous women to have pelvic organ prolapse. Causes of pelvic support disorders are most likely multifactorial, however; factors other than vaginal delivery also are associated with the development of these disorders. One study found that the incidence of prolapse doubled with each decade of life between the ages of 20 and 59 years (8). In another study, each year of increasing age was associated with a 12% increase in the risk of developing prolapse (9). Other associated risk factors for the development of POP include history of hysterectomy (8), obesity (7,10,11), history of previous prolapse operations, and race (11).

Pathophysiology

Pelvic organ prolapse results from attenuation of the supportive structures, whether by actual tears or "breaks" or by neuromuscular dysfunction or both. Support of the vaginal canal is provided by the enveloping endopelvic connective tissue and its condensations at the vaginal apex, which form the cardinal uterosacral ligament complex. The endopelvic connective tissue is the first line of support buttressed intimately with the pelvic diaphragm, composed of the levator ani and coccygeus muscles. These muscles provide a supportive diaphragm through which the urethra, vagina, and rectum egress (Fig. 24.1). The muscular support provides basal tonicity and support of the pelvic structures; when contracted as in the setting of increased abdominal pressure, the rectum, vagina and urethra are pulled anteriorly toward the pubis.

Definitions

The more common pelvic support disorders include **rectoceles** and **cystoceles** (Fig. 24.2), **enteroceles** (Fig. 24.3), and **uterine prolapse** (Fig. 24.4), reflecting displacement of the rectum, small bowel, bladder, and uterus, respectively, resulting from failure of the endopelvic connective tissue, levator ani muscular support, or both.

A **rectocele** is a protrusion of the rectum into the vaginal lumen resulting from weakness in the muscular wall of the rectum and the paravaginal musculoconnective tissue, which holds the rectum in place posteriorly.

An **enterocele** is a herniation of the peritoneum and small bowel and is the only true hernia among the pelvic support disorders. Most enteroceles occur downward between the uterosacral ligaments and the rectovaginal space, but they may also occur primarily apically, especially in the setting of a previous hysterectomy.

A **cystocele** is a herniation of the urinary bladder through the anterior vaginal wall. Cystoceles usually occur when the pubocervical musculoconnective tissue weakens midline or detaches from its lateral or superior connecting points.

Uterine prolapse is generally the result of poor cardinal or uterosacral ligament apical support, which allows downward protrusion of the cervix and uterus toward the introitus.

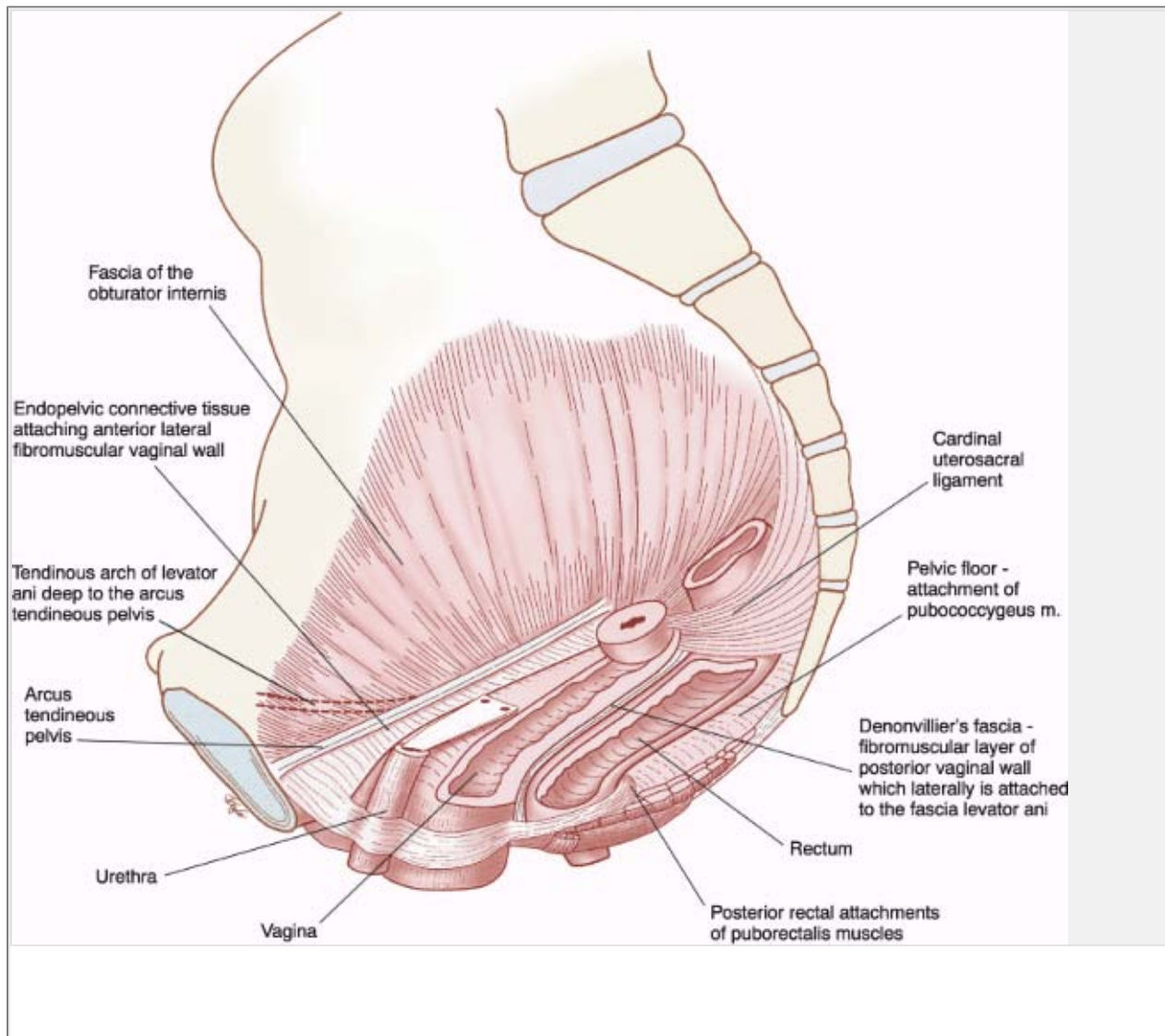


Figure 24.1 A sagittal view of the female pelvis with bladder and uterus removed (ureters, trigone, and cervix intact) illustrating anterior and posterior vaginal fibromuscular planes, their endopelvic fascial attachments, and a functional pelvic floor. (Redrawn by J. Taylor from Skandalakis JE et al., eds. *Hernia: Surgical Anatomy and Technique*, 244–250.)

Procidentia, which involves prolapse of the uterus and vagina, and *total vaginal vault prolapse*, which can occur after hysterectomy, represent eversion of the entire vagina (Fig. 24.5).

These descriptive terms are somewhat inaccurate and misleading, focusing on the bladder, rectum, small bowel, or uterus rather than the specific defects responsible for the alterations in vaginal support. Specific defect support issues will be discussed in the setting of the surgical management section.

Evaluation

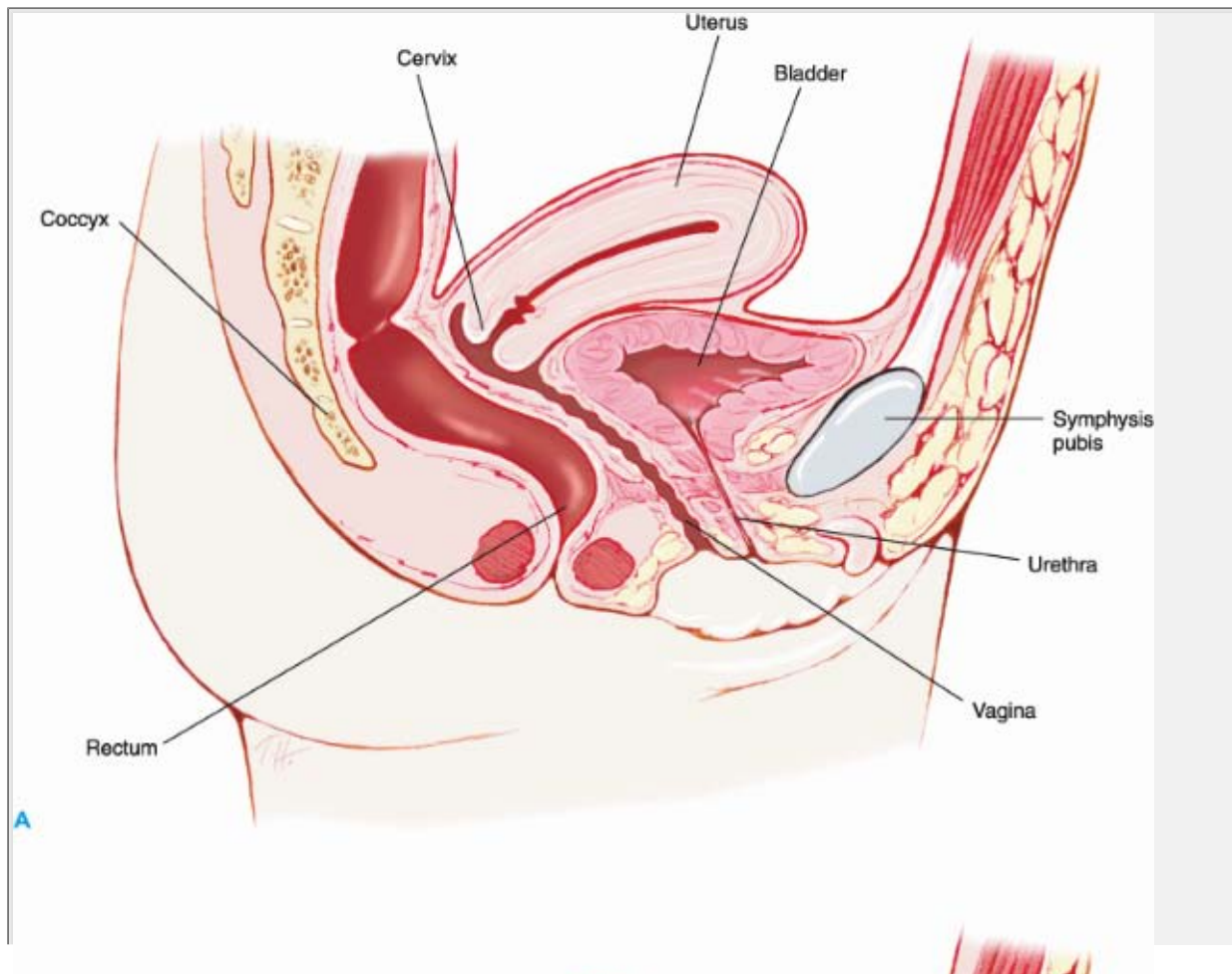
Although as many as 50% of women older than age 50 have some degree of pelvic organ prolapse (12), fewer than 20% seek treatment (13). This may be due to a number of reasons, including lack of symptoms, embarrassment, or misperceptions

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about available treatment options. Although pelvic organ prolapse is not life threatening, it can impose a significant burden of social and physical restrictions of activities, impact on psychological well-being, and overall quality of life.



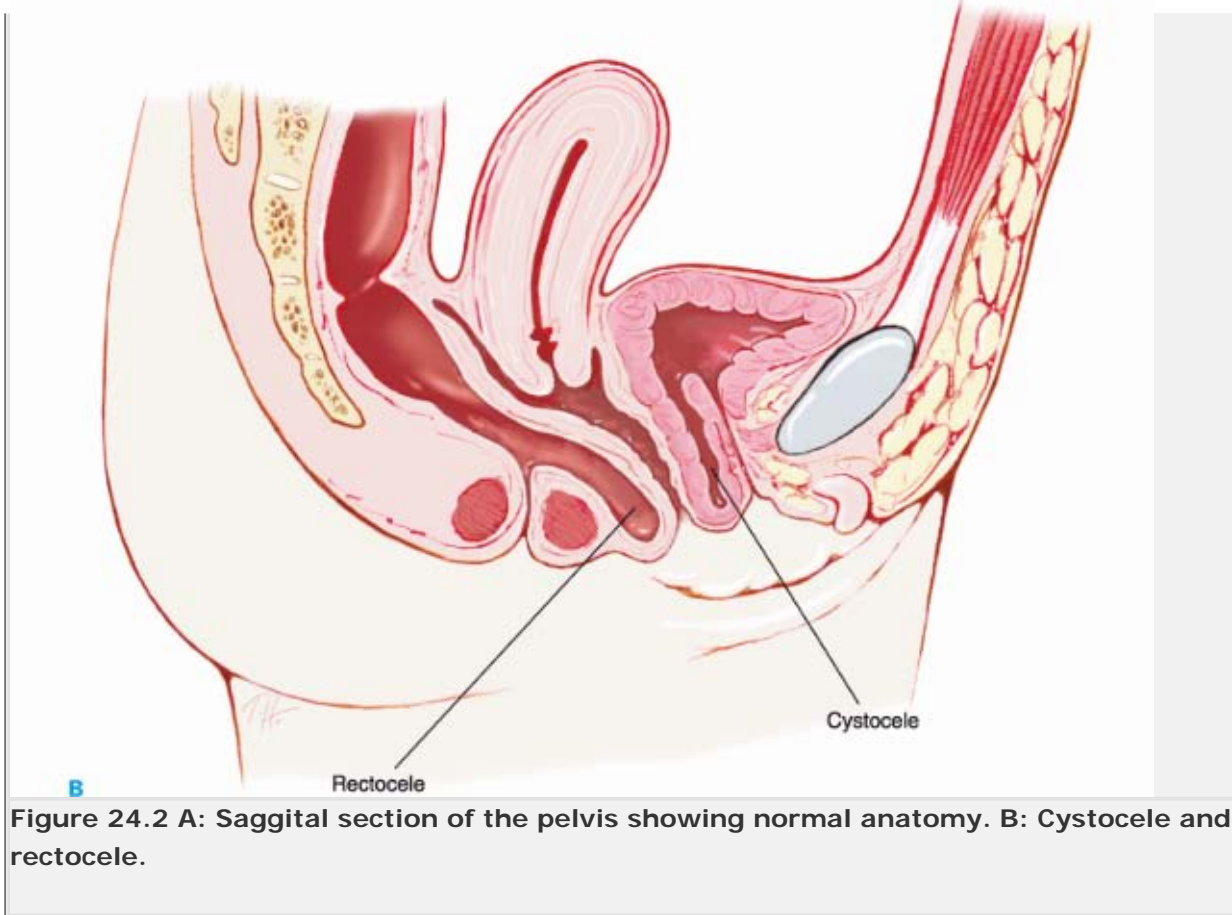
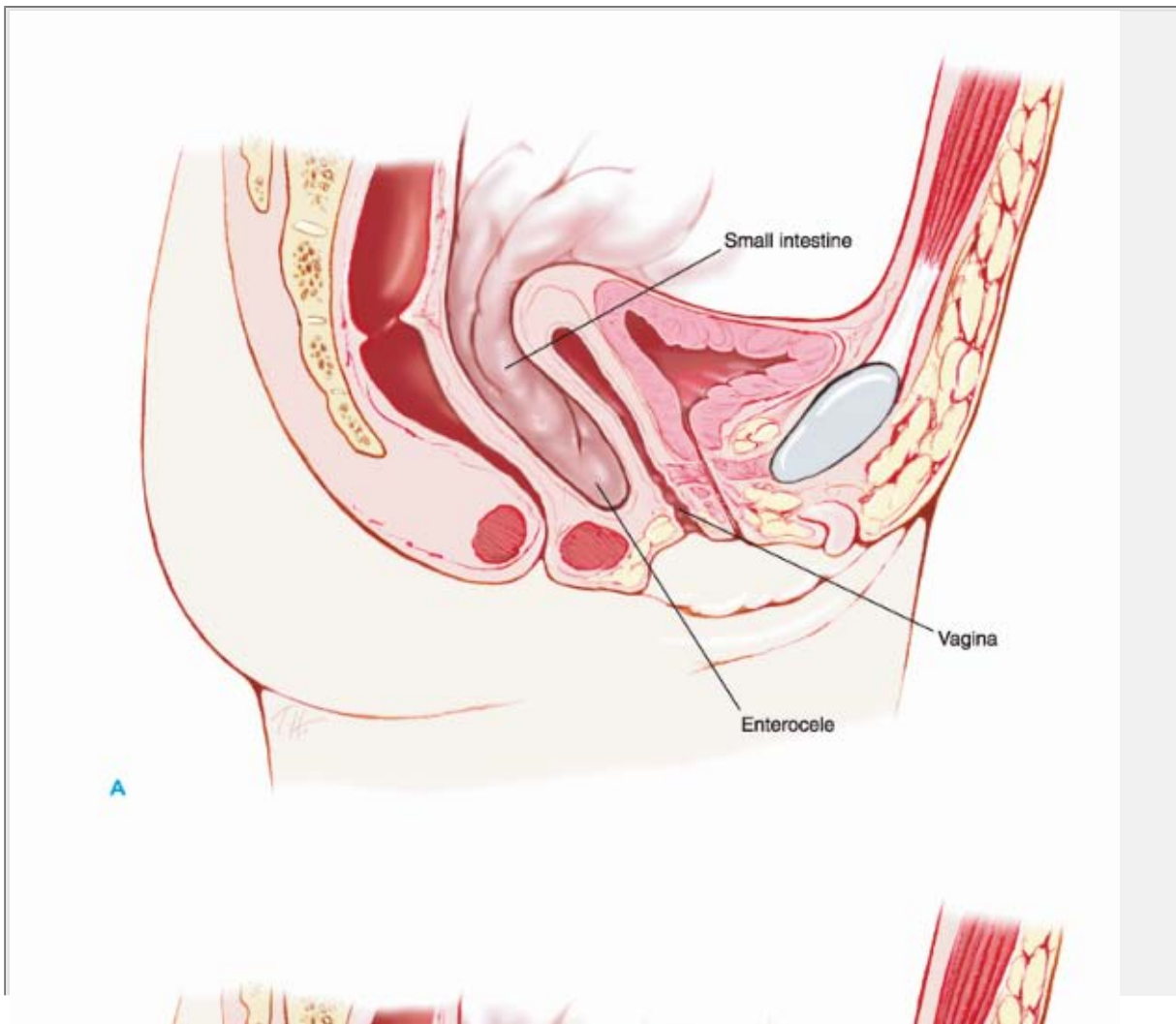


Figure 24.2 A: Saggital section of the pelvis showing normal anatomy. B: Cystocele and rectocele.



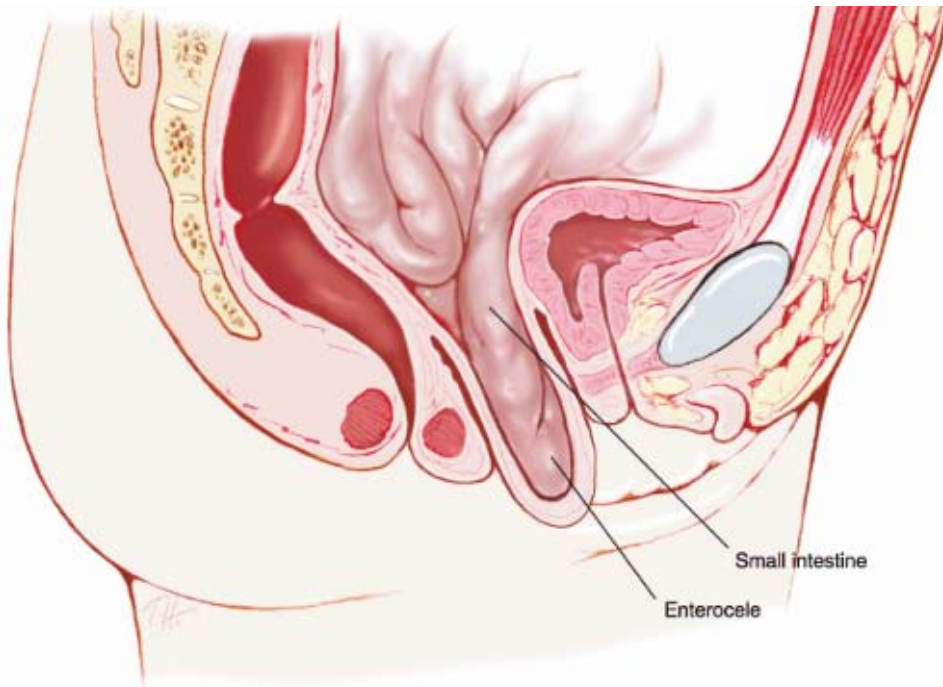


Figure 24.3 A: Posterior enterocele without eversion. B: Enterocele with eversion.



Figure 24.4 Uterine prolapse with apical detachment from the uterosacral ligament complex and lateral wall detachment from the endopelvic connective tissue.

Symptoms

Pelvic organ prolapse often is accompanied by symptoms of voiding dysfunction, including urinary incontinence, obstructive voiding symptoms, urinary urgency and frequency, and, at the extreme, urinary retention and upper renal compromise with resultant pain or anuria. Other symptoms often associated with POP include pelvic pain, defecatory problems (e. g., constipation, diarrhea, tenesmus, fecal incontinence), back and flank pain, overall pelvic discomfort, and dyspareunia. Patients seeking care for prolapse may have one or several of these symptoms involving the lower pelvic floor. **Choice of treatment usually depends on severity of the symptoms and the degree of prolapse consistent with the patient's general health and level of activity.**

Data relating pelvic floor symptoms to the extent and location of prolapse are weak (14,15,16). Any symptoms associated with physical findings of lower stage prolapse require careful evaluation, especially if surgery is being considered. A recent retrospective study of 330 patients reported that women with more advanced prolapse were less likely to have symptoms of stress incontinence and more likely to use manual reduction of the prolapse to void. Therefore, careful consideration of lower urinary tract symptoms

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is important. Prolapse severity was not associated with bowel or sexual problems in this study (17).



Figure 24.5 Procidentia of the uterus and vagina.

Physical Examination

In evaluating patients with pelvic organ prolapse, it is particularly useful to divide the pelvis into compartments, each of which may exhibit specific defects. The use of a Graves speculum or Baden retractor can help to evaluate the apical compartment of the vagina. The anterior and posterior compartments are best examined with the use of a univalve or Sims' speculum. The speculum is placed posteriorly to retract the posterior wall downward when examining the anterior compartment and placed anteriorly to retract the anterior wall

upward when examining the posterior compartment. A rectovaginal examination may be useful in evaluating the posterior compartment to distinguish a posterior vaginal wall defect from a dissecting apical enterocele or a combination of both.

If an anterior lateral detachment defect is suspected, an open ring forceps (or a Baden retractor) may be placed in the vagina at a 45-degree angle posteriorly cephalad to hold the lateral fornices adjacent to the pelvic sidewall.

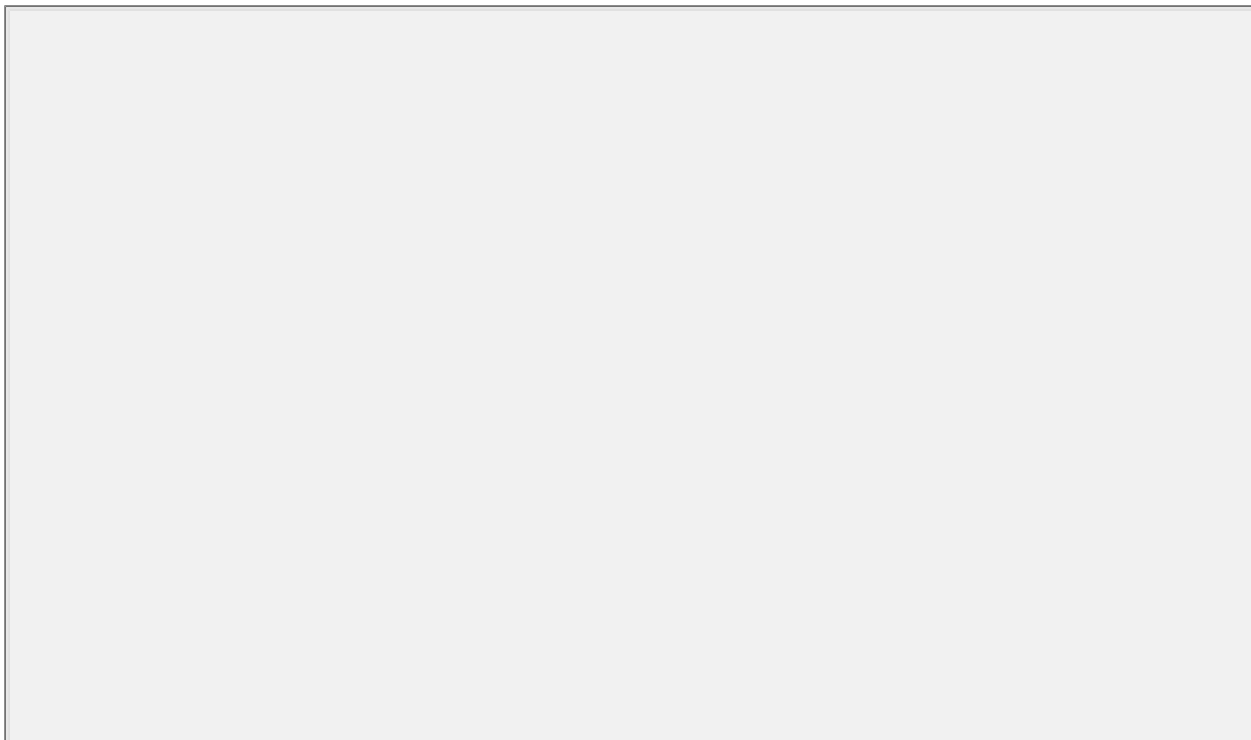
During the evaluation of each compartment, the patient is encouraged to perform Valsalva so the full extent of the prolapse can be ascertained. If the findings determined with Valsalva are inconsistent with the patient's description of her symptoms, it may be helpful to perform a standing straining examination with the bladder empty (18).

Pelvic Organ Prolapse Quantitation System

Many systems for staging prolapse have been described. Typically it is graded on a scale of 0 to 3 or 0 to 4, with the grade increasing with the severity of prolapse (19,20). **Currently the system approved by the International Continence Society is the Pelvic Organ Prolapse Quantification system, or POP-Q (21).** This standardized quantification system facilitates communication between physicians in practice and research and enables progression of these conditions to be followed accurately. In this system, anatomic descriptions of

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specific sites in the vagina are used in place of traditional terms. The system identifies nine locations in the vagina and vulva in centimeters relative to the hymen, which are used to assign a stage (from 0 to IV) of prolapse at its most advanced site (Fig. 24.6). Although probably more detailed than necessary for general practice, clinicians should be familiar with the POP-Q system because most published studies use it to describe research results. Its two most important advantages over previous grading systems are (i) it allows the use of a standardized technique with quantitative measurements at straining relative to a constant reference point (i.e., the hymen), and (ii) its ability to assess prolapse at multiple vaginal sites.



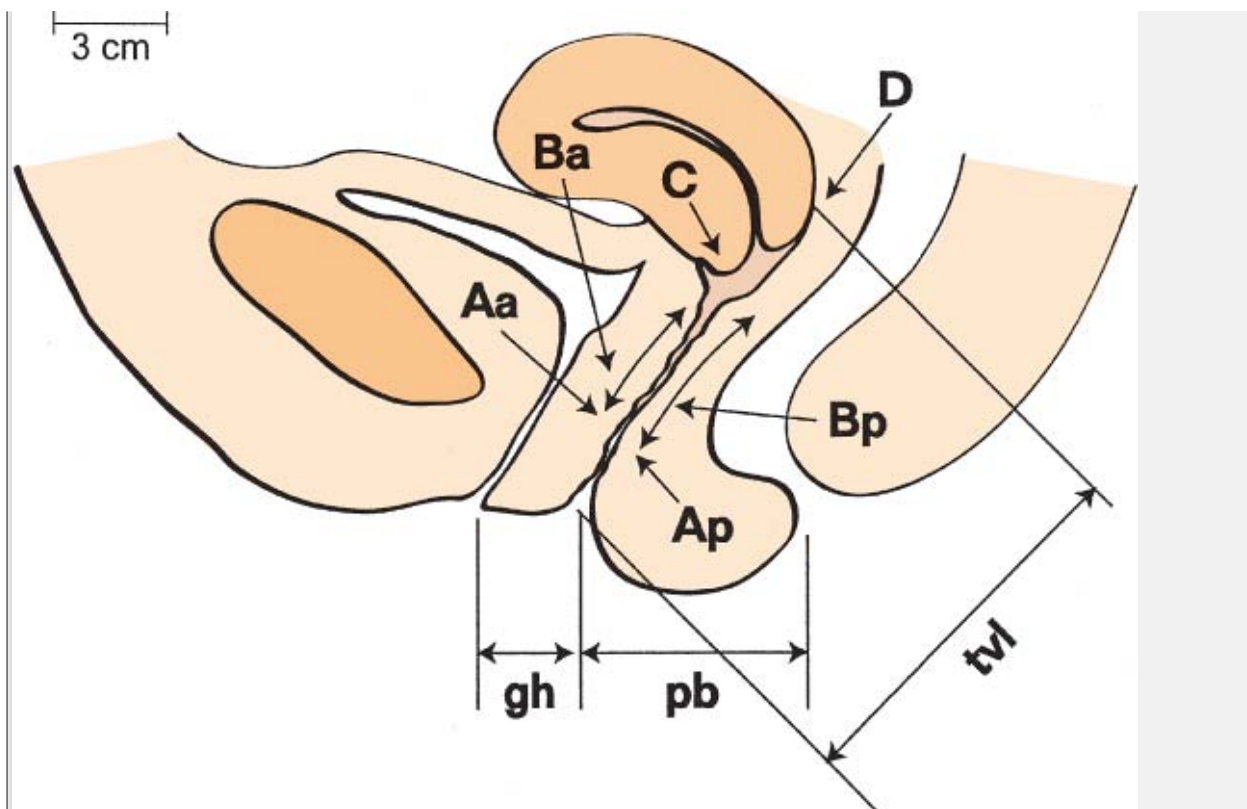


Figure 24.6 Standardization of terminology for female pelvic organ prolapse (POP-Q classification). This diagram demonstrates the anatomic position of the POP-Q sites, including six sites involving the anterior (Aa, Ba), middle (C, D), and posterior (Ap, Bp) compartments with the genital hiatus (gh), perineal body (pb), and total vaginal length (tvl). (From **Bump RC, Mattiason A, Bo K, et al.** The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996; 175: 12, with permission.)

The classification uses six points along the vagina (two points on the anterior, middle, and posterior compartments) measured in relation to the hymen. The anatomic position of the six defined points should be measured in centimeters proximal to the hymen (negative number) or distal to the hymen (positive number), with the plane of the hymen representing zero. Three other measurements in the POP-Q examination include the genital hiatus, perineal body, and the total vaginal length.

The genital hiatus is measured from the middle of the external urethral meatus to the posterior midline hymen. The perineal body is measured from the posterior margin of the genital hiatus to the midanal opening. The total vaginal length is the greatest depth of the vagina in centimeters when the vaginal apex is reduced to its full normal position. All measurements except the total vaginal length are measured during maximal straining.

The anterior vaginal wall measurements are termed Aa and Ba, with the Ba point moving depending on the amount of anterior compartment prolapse. Point Aa

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represents a point on the anterior vagina 3 cm proximal to the external urethral meatus, which corresponds to the bladder neck. By definition, the range of position of this point is -3 to +3. Point Ba represents the most distal or dependent point of any portion of the anterior vaginal wall from point Aa to just anterior to the vaginal cuff or anterior lip of the cervix. This point can vary depending on the nature of the patient's support defect. For example, point Ba is -3 in the absence of any prolapse (it is never less than -3) to a positive value equal to the total

vaginal length in a patient with total eversion of the vagina.

Table 24.1 Possible Ranges of the Six Site-specific Pelvic Organ Prolapse Quantitative Examination Measurements

<i>Points</i>	<i>Description</i>	<i>Range</i>
Aa	Anterior wall 3 cm from hymen	-3 cm to +3 cm
Ba	Most dependent portion of rest of anterior wall	-3 cm to +TVL
C	Cervix or vaginal cuff	±TVL
D	Posterior fornix (if no prior hysterectomy)	±TVL or omitted
Ap	Posterior wall 3 cm from hymen	-3 cm to +3 cm
Bp	Most dependent portion of rest of posterior wall	-3 cm to +TVL

TVL, total vaginal length.

Adapted from **Bump RC, Mattiasson A, Bo K, et al.** The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:11–12, with permission.

The middle compartment consists of points C and D. Point C represents the most dependant edge of the cervix or vaginal cuff after hysterectomy. Point D is the location of the posterior fornix; it is omitted if the cervix is absent. This point represents the level of the attachment of the uterosacral ligament to the posterior cervix. It is intended to differentiate suspensory failure from cervical elongation.

The posterior compartment is measured similarly to the anterior compartment: the corresponding terms are Ap and Bp. The nine measurements can be recorded as a simple line of numbers (i.e., -3, -3, -8, -10, -3, -3, 11, 4, 3 for points Aa, Ba, C, D, Ap, Bp, total vagina length, genital hiatus, and perineal body). The six vaginal sites have possible ranges that depend on the total vaginal length (Table 24.1). After collection of the site-specific measurements, stages are assigned according to the most dependent portion of the prolapse (Table 24.2). The POP-Q examination often appears confusing on initial review; however, a measuring device (i.e., a marked ring forceps or marked cotton-tip applicator) can assist

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in instructing those unfamiliar with this staging system. The POP-Q examination provides a standardized measurement system to allow for more accurate assessments of postoperative outcome and to ensure uniform, reliable, and site-specific descriptions of pelvic organ prolapse. A videotape describing the system and showing its use in several patients is available from the American Urogynecology Society.

Table 24.2. Stages of Pelvic Organ Prolapse

Stage 0	No prolapse is demonstrated. Points Aa, Ap, Ba, Bp are all at -3 cm, and point C is between total vaginal length (TVL) and -(TVL -2 cm).
Stage I	The most distal portion of the prolapse is >1 cm above the level of the hymen.
Stage II	The most distal portion of the prolapse is <1 cm proximal or distal to the plane of the hymen.
Stage III	The most distal portion of the prolapse is <1 cm below the plane of the hymen but no further than 2 cm less than the total vaginal length.
Stage IV	Complete to nearly complete eversion of the vagina. The most distal portion of the prolapse protrudes to > + (TVL -2) cm.

From **Bump RC, Mattiassion A, Bo K, et al.** The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:13, with permission.

In a clinical setting, at least three measurements should be obtained: the most advanced extent of the prolapse in centimeters relative to the hymen that affects the anterior vagina, the posterior vagina, and the cervix or vaginal apex.

As noted previously, whether the older staging systems or the POP-Q system is used, **it is important to document the most pertinent findings on examination. This will help in documenting the baseline extent of prolapse and the results of treatment.**

Pelvic Muscle Function Assessment

Pelvic muscle function should be assessed during the pelvic examination. Following bimanual examination with the patient in lithotomy position, the examiner can palpate the puborectalis muscle inside the hymen along the pelvic sidewalls at approximately the 4 and 8 o'clock positions. One can appreciate basal muscle tone and whether there is increased tone with contraction as well as strength, duration, and symmetry of contraction (22). **A rectovaginal examination should also be performed to assess basal and contraction muscle tone of the anal sphincter complex.**

As a part of the pelvic organ prolapse examination, urethral mobility often is measured. Many women with prolapse will have urethral hypermobility (defined as a resting urethral angle greater than 30 degrees or a maximal strain angle greater than 30 degrees). The presence of urethral mobility in combination with symptoms of stress incontinence may help determine whether an incontinence procedure should be performed. During pelvic examination, the urethra is typically swabbed with Betadine, and lidocaine jelly is placed in the urethra or on a cotton tip swab. The swab is placed in the urethra at the urethrovesical junction and with the use of a goniometer (Fig. 24.7), and the baseline urethral angle from the horizontal and maximal strain angles are measured.

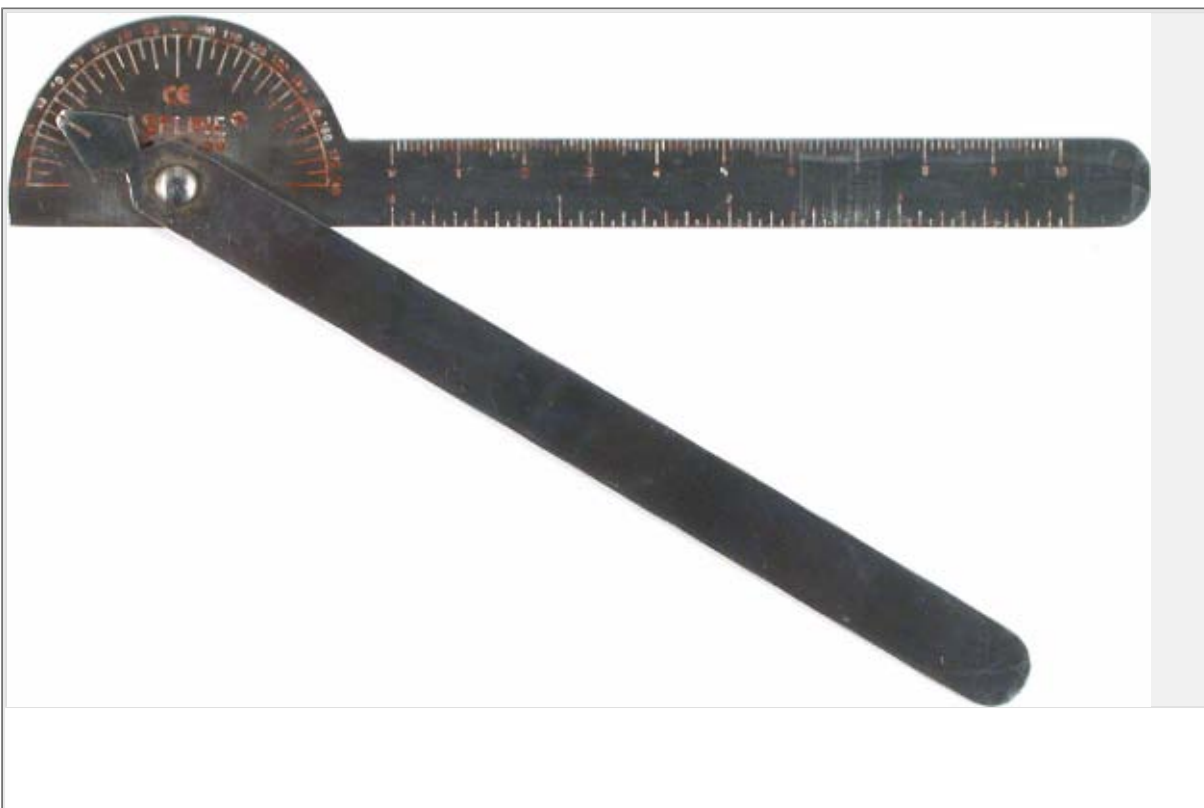


Figure 24.7 Goniometer, which is used to measure baseline urethral angle and maximal strain angle of the urethra with a Q-tip in place.

Bladder Evaluation

Patients with prolapse exhibit the full range of lower urinary tract symptoms. Despite the fact that some patients may not have significant symptoms, it is important to obtain objective information about bladder and urethral function. With severe POP, the urethral kinking effect of the prolapse may mask a potential urine leakage problem; therefore, basic office bladder testing with prolapse reduction should be performed to mimic bladder and urethral function if the prolapse were treated. At a minimum, the following assessments should be performed: a clean catch or catheterized urine sample to test for infection, a postvoid residual (PVR) volume, and assessment of bladder sensation, which can be performed as a part of office cystometrics. Although there is no consensus on what constitutes an abnormal PVR volume, provided the patient has voided 150 mL or more, a PVR less than or equal to 100 mL is acceptable. Reduction stress testing at the time of simple office cystometrics can be performed with the use of a pessary, large cotton swab, ring forceps, or the posterior blade of a speculum. Care should be taken that the urethra not be overly straightened (with a resultant false-positive test result) or obstructed (with a resultant false-negative test result), or that tension is not placed on the puborectalis muscles by excessive posterior retraction. These risks can be minimized by orienting the vaginal apex toward the sacrum.

Imaging

Diagnostic imaging of the pelvis in women with pelvic organ prolapse is not routinely performed. However, if clinically indicated, tests that may be performed include fluoroscopic evaluation of bladder function, ultrasound of the pelvis, and defecography for patients in whom intussusception or rectal mucosal prolapse are suspected. Magnetic resonance imaging is increasingly being used for the evaluation of pelvic pathology such as mullerian anomalies and pelvic pain, however, generalized use in women with prolapse is not currently clinically indicated and is used primarily for research purposes.

Treatment

Nonsurgical Therapy

Nonsurgical therapy of pelvic organ prolapse includes conservative behavioral management and the use of mechanical devices. **A nonsurgical treatment approach usually is considered in women with mild to moderate prolapse, those who desire preservation of future childbearing, those in whom surgery may not be an option, or those who do not desire surgical intervention.**

Conservative Management

Conservative management approaches include alteration of lifestyle or physical intervention such as **pelvic floor muscle training (PFMT)**. These approaches are used mainly in cases of mild to moderate prolapse; however, their true role in managing prolapse and associated symptoms is unclear (23,24). The goals of a conservative therapy approach to the treatment of prolapse are as follows (25):

- Prevent worsening prolapse
- Decrease the severity of symptoms
- Increase the strength, endurance, and support of the pelvic floor musculature
- Avoid or delay surgical intervention

Lifestyle intervention includes such activities as weight loss and reduction of those activities that increase intra-abdominal pressure. This interaction is typically anecdotal in practice. No case series, prospective studies, or randomized control trials exist that have examined the effectiveness of this approach to the treatment of prolapse.

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Pelvic floor muscle exercises may limit the progression of mild prolapse and related symptoms (26,27); however, a lower response rate has been noted when prolapse extends beyond the vaginal introitus (28).

The efficacy of biofeedback therapy in the treatment of impaired defecation associated with a rectocele has been determined (29). Thirty-two female patients, median age 52 years (range, 34–77 years), experiencing impaired rectal evacuation with a rectocele greater than 2 cm at proctography underwent a structured behavioral retraining. Immediate and medium-term follow-up results were reported (median 10 months; range 2–30 months). Fifty-six percent of patients ($n = 14$) felt a little and 16% ($n = 4$) felt major improvement in symptoms, including 3 (12%) with complete symptom relief. Immediately after biofeedback there was a modest reduction in need to strain (72; 50%), feeling of incomplete evacuation (78; 59%), and need to assist defecation digitally (84; 63%) that was maintained at follow-up. Bowel movement frequency was significantly normalized at follow-up ($p = 0.02$). These investigators concluded that **behavioral retraining, including biofeedback therapy, may be an effective primary therapy for some patients with a rectocele associated with impaired defecation.**

Mechanical Devices

The use of mechanical devices such as pessaries is usually considered in women who for medical reasons cannot undergo surgery, desire to avoid surgery, or have a significant degree of prolapse that makes other nonsurgical approaches unfeasible.

Some practitioners extend indications to include pregnancy-related prolapse as well as prolapse and incontinence in elderly women. Reports have shown that age older than 65 years, the presence of severe medical comorbidity (30), and sexual activity (31) were associated with successful pessary use. Unsuccessful use or a desire for surgery has been associated with a shortened vaginal length (≤ 6 cm), a wide vaginal introitus (32), sexual activity, stress incontinence, stage III–IV posterior compartment prolapse, and desire for surgery at a first office visit. Few literature-based reviews and reports recommend pessaries as first-line treatment for women with POP, and there is little consensus regarding choice of pessary and management of pessary usage (33). Most of the information on pessary use is derived primarily from descriptive and retrospective studies, relatively small prospective series, manufacturer's recommendations, and anecdotal experience.

Pessaries provide pelvic organ support within the vaginal vault. **Two categories of pessaries—support and space filling—exist for prolapse (33). The ring pessary (with diaphragm) is a commonly used support pessary, and the Gelhorn pessary is a commonly used space-filling pessary. The ring and other support pessaries are recommended for stage I and II prolapse, whereas the space-filling pessaries are used for stage III and IV prolapse (34).** It is unclear whether pessaries with regular use can prevent the progression of POP. A prospective cohort study addressed this issue in a series of 56 women who were fit with a pessary, of which 33.9% (n = 19) continued use for at least 1 year (35). Baseline and follow-up pelvic examinations were performed using the POP-Q system (21). The women removed the pessary 48 hours before one visit, but there was no information to ascertain adherence to pessary use. No woman had worsening of the prolapse, and four women (21.1%, 95% CI 0.2, 43.7%) had an improvement. Improvement overall was noted in women with anterior compartment prolapse.

There are no randomized controlled trials of pessary use in women with POP (36). Likewise, there are no consensus guidelines on the care of pessaries (i.e., intervals between changes), the role of local estrogens, or the type of pessary indicated for specific types of POP (36). Manufacturers recommendations and different pessary types can be seen in Figure 24.8. Effective and satisfactory outcomes have been reported for stage II or greater prolapse using the Gelhorn and ring diaphragm pessary (30). After 2 to 6 months, 77% to 92% of women with a successful pessary fitting were satisfied and, using intention-to-treat analysis, 44% to 67% of all women who were treated initially with a pessary for prolapse

P.909

were satisfied. There are few other series describing pessary use for prolapse with greater than 4 weeks follow-up (37,38,39,40,41).



R Shaatz (Silicone) **S** Incontinence Dish with Support (Silicone) **T** Ring Incontinence (Silicone) **U** Ring (Silicone)

V Incontinence Dish (Silicone) **W** Inflatoball (Latex) **X** Donut (Silicone)

Figure 24.8 Pessaries used to treat the various degrees of prolapse (Milex Company, a Division of Cooper Surgical).

Possible complications associated with pessary use include vaginal discharge and odor. Failure to retain the pessary may occur or, conversely, the pessary may be too large, which could lead to excoriation or irritation. With reduction of vaginal prolapse, *de novo* or increased stress incontinence may occur (42), and in rare instances, more severe complications, including vesicovaginal fistula, small bowel entrapment, hydronephrosis, and urosepsis, have been described (43,44).

Placement and Management

Pessary placement involves consideration of a number of issues, primarily the patient's desire and motivation to use this type of device. Typically, if she has had previous surgery or strongly desires to avoid surgery, she may be motivated enough for a primary attempt at pessary placement. Other issues include current sexual function status, type and duration of exercise in which the patient engages, and the status of the vaginal walls and cervix.

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In hypoestrogenic women, treatment of the vagina with estrogen and maintenance of intravaginal estrogen treatment is recommended.

Fitting a Pessary

The patient should be examined in the lithotomy position after emptying her bladder. The clinician should use a dry glove to better grasp the pessary and water-soluble lubricants as needed. The size of the pessary is estimated after a digital examination and use of ring forceps to reduce the prolapse or bladder neck. Once the approximate size is determined, the appropriate type is selected based on the patient's needs and activity level. **When fitted, the patient is asked to stand, perform Valsalva, and cough to ensure the pessary is retained.** The pessary should be assessed to ensure it is providing the desired support and leakage control. The patient should be able to void with the pessary in place before leaving the office. Proper size is assured by the ability to sweep the index finger between the pessary and the vaginal wall. The patient should feel comfortable with the pessary in place.

Insertion of the pessary is eased by using a water-soluble lubricant for insertion, folding or collapsing the pessary to reduce its size, and when it is inside the vagina, pushing it high to an area behind the symphysis pubis and inserting the device more posteriorly to avoid the urethra. Instructing the patient how to insert and remove the pessary may be done with the patient in a standing or supine position, depending on her dexterity (41,45).

Ring pessaries, with or without support, are the most commonly used type. They are the easiest to fold, insert, and remove. **Gellhorn** and **cube** pessaries are typically more difficult to insert and remove by the patient. They are held in place by significant space occupation and suction and offer strong support. The suction of the cube pessary needs to be broken, facilitating removal. Cube pessaries should be removed daily; Gelhorns can stay in longer (up to 6–8 weeks). **Donut pessaries**, which are very popular, are considered a space-fitting pessary for large vaginal vault prolapse, complete procidentia with decreased perineal support, and good introital integrity. **The patient should be questioned about a latex allergy and instructed to remove and clean the device every 2 to 3 days.** Continence pessaries, rings,

and dishes with support typically also are easy to fold, insert, and remove (46).

Follow-Up Recommendations

After the initial fitting, the patient should return in 1 to 2 weeks and then at 4 to 6 weeks, depending on her independence with the pessary, her proficiency in placement and removal, and her cognitive and motor abilities (38). After this initial follow-up, continued follow-up should continue at 6- to 12-month intervals at the discretion of the provider and depending on the patient's ability to insert and remove the pessary effectively. If the patient needs to return to the provider for removal and cleaning of the pessary, 4- 12-week intervals are more appropriate.

On follow-up visits, proper placement of the pessary and support of the prolapse as well as continence efficacy should be assured. Because pessaries are fit by a process of trial and error, it is not uncommon to change the size or type at least once after the initial fitting. The pessary's integrity should be checked, and the tissue for evaluated for irritation, pressure sores, ulceration, and lubrication.

Surgical Management

The primary aims of surgery are to relieve symptoms, which may be caused by prolapse, and, in most cases, to restore vaginal anatomy so that sexual function may be maintained or improved without significant adverse effects or complications. Occasionally, when sexual function is not desired, obliterative or constrictive surgery is more appropriate and also may relieve symptoms. There is no steadfast rule as to when

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surgery is indicated. Many patients with more advanced prolapse have few or no symptoms, whereas some with lesser degrees of prolapse have what they term *severe symptoms*. This is confounded by the observation that many of the "symptoms" may not be specifically related to the anatomic defect or may be worsened by anxiety. In general, surgery should be offered to patients who have tried conservative therapy and were not satisfied with the results or who do not desire conservative therapy. The prolapse should be symptomatic or should be greater than or equal to stage II with apparent progression. All patients should be given the alternative of trying conservative treatments when applicable.

Approaches to surgery include vaginal, abdominal, and laparoscopic routes, or a combination of approaches. Depending on the extent and location of prolapse, surgery may involve a combination of repairs directed to the anterior vagina, vaginal apex, posterior vagina, and perineum. Concomitant surgery may be planned for urinary or fecal incontinence. The surgical route is chosen based on the type and severity of prolapse, the surgeon's training and experience, the patient's preference, and the expected or desired surgical outcome.

Procedures for prolapse can be broadly categorized into three groups: (i) restorative, which use the patient's endogenous support structures; (ii) compensatory, which attempt to replace deficient support with permanent graft material; and (iii) obliterative, which close or partially close the vagina.

These groupings are somewhat arbitrary and not entirely exclusive. For example, grafts may be used to reinforce repairs such as colporrhaphy, or to replace support that is deficient or lacking. Graft use in sacrocolpopexy substitutes for the connective tissues attachments (cardinal and uterosacral ligaments) that would normally support the vaginal apex. In addition to the primary goal of relieving symptoms related to prolapse, urinary, defecatory, and sexual function must be considered in choosing the appropriate procedures. The following section includes

a review of (i) the anatomy of pelvic support structures, (ii) the defects related to these structures, and (iii) some of the most commonly used surgical procedures to correct these defects.

Basic Anatomy of Support Structures

Pelvic support structures include:

- The muscles and connective tissue of the pelvic floor
- The fibromuscular tissue of the vaginal wall
- The endopelvic connective tissue

The endopelvic connective tissue includes:

- The cardinal/uterosacral complex, which attaches the upper vagina and cervix posteriorly
- Lateral connective tissue attachments of the anterior vaginal wall to the arcus tendineus pelvis and of the posterior vaginal wall to the fascia of the levator ani and to the posterior arcus tendineus near the ischial spine
- Less dense areolar connective tissue surrounding retroperineal portion of the pelvic organs

The orientation of these structures is noted in Figure 24.1. In general, an intact pelvic floor, including a functional puborectalis muscle and an intact cardinal/uterosacral complex, should prevent pelvic organ prolapse by allowing posterior deflection of the rectum and

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vagina, and compression of these structures against the pelvic floor in the upright position (Fig. 24.9). The fibromuscular layer of the vaginal wall and the other endopelvic connective tissue attachments augment the support structure and are particularly important when pelvic floor function is compromised.

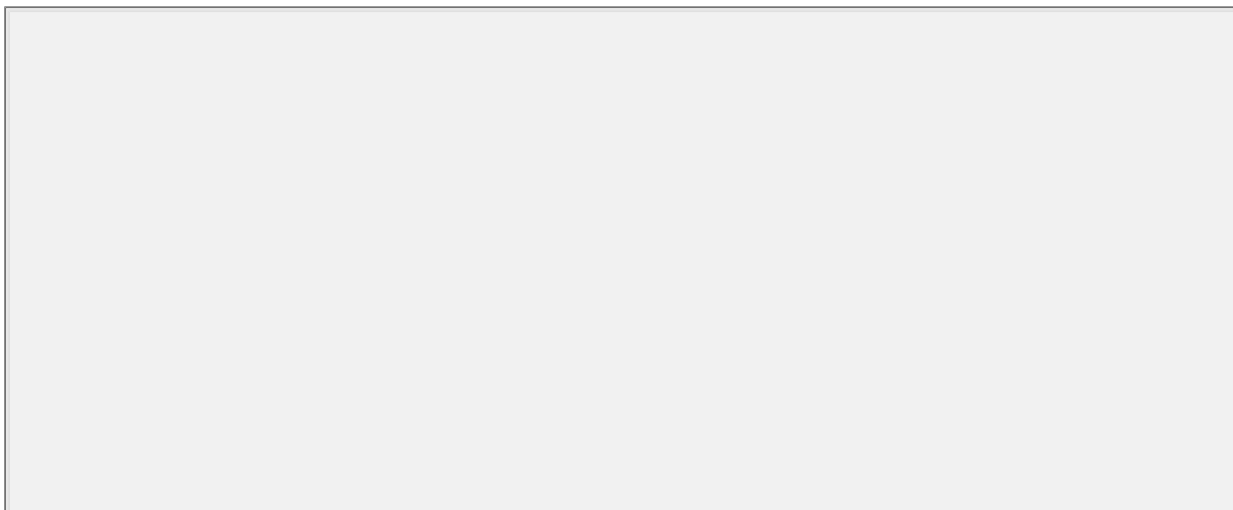




Figure 24.9 Vaginograms from the same patient at rest (A) and during Valsalva maneuver (B). Illustrates posterior vaginal deflection maintained by apical cardinal/uterosacral posterior suspension and the anterior sling effect of the puborectalis muscle and more distal perineal structures. (From **Nichols DH, Randall CL.** *Vaginal surgery.* 4th ed. Baltimore, MD: Williams & Wilkins, 1996: 4–5.)

Whether to repair all defects is controversial. Restorative repairs may be less successful than compensatory repairs in patients with generally “poor tissue,” and at times one defect repair may exert more tension on the repair of another defect. Management should be based on the patient's presentation, expectations, the specific anatomical defects noted (preoperatively and, at times, intraoperatively), and on the presence or absence of lower urinary and bowel dysfunction.

The Anterior Compartment

The anterior vaginal compartment includes the anterior vaginal wall, its attachments, the urethra, and the bladder. The support structure for the bladder is the rhomboid-shaped anterior vaginal wall (specifically its fibromuscular layer), which is attached laterally to the arcus tendineus fascia (Fig. 24.10). Inferiorly, the fibromuscular layer blends in with the connective tissue, which spans the two bands of puborectalis and pubococcygeus muscles and the pubic rami. The urethra appears to be preferentially supported by these connective tissues as well as by the pubourethral ligaments, which have debatable function. In the apical area, the vaginal fibromuscular layer blends in with the precervical fascia and the connective tissue of the cardinal ligament complex. In the upright position, the rhomboid-shaped anterior vaginal wall is oriented approximately

30 degrees from the horizon (from pubis to ischial spines). There is some downward bulge of the central area of the rhomboid plate, which should be minimized by the back-stop effect of the posterior vagina and rectum if the pelvic floor anatomy and function are normal.

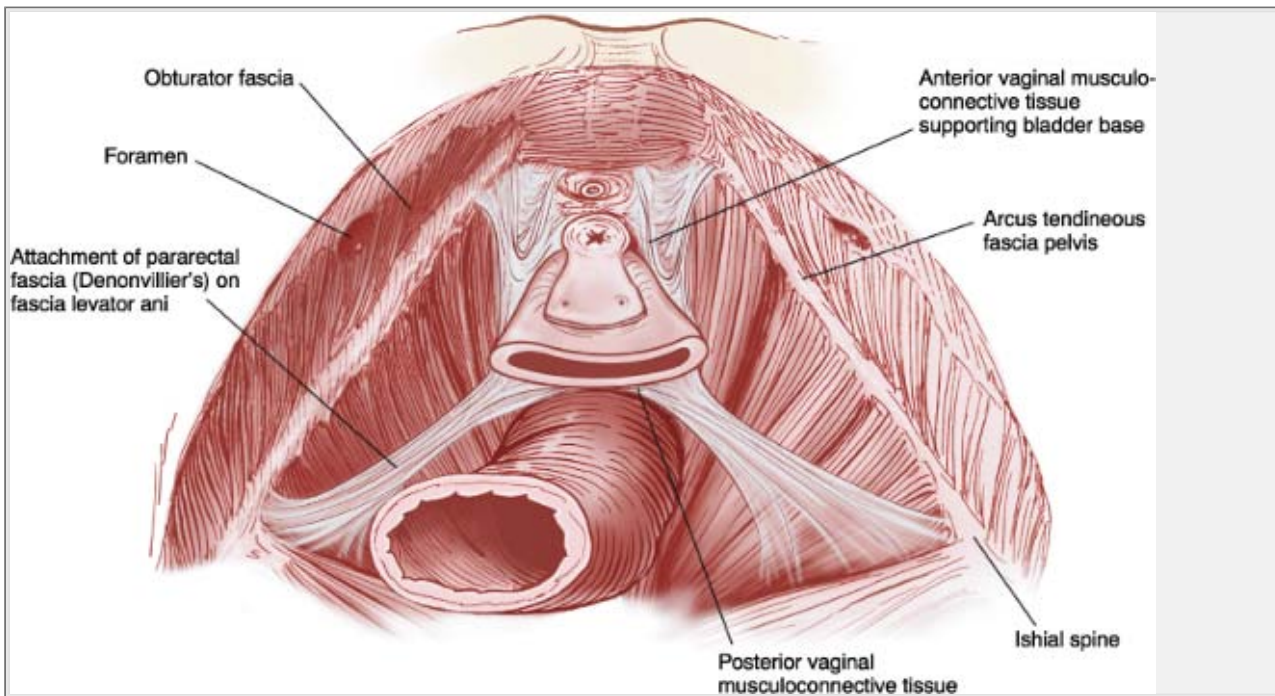


Figure 24.10 View of the pelvic cavity with bladder, upper vagina, and sigmoid colon removed. The fibromuscular wall of the anterior vagina is attached to the arcus tendineus fascia pelvis by endopelvic connective tissue and supports the bladder. The pararectal fascia (Denonvillier's fascia) includes the fibromuscular tissue of the posterior vagina and its lateral attachment to the fascia levator ani.

Defects of this support structure may include tears or attenuation of the vaginal fibromuscular wall, or detachment from the pelvic sidewalls, the cervix or cardinal ligament complex, or from the pubis. Specific sites of fibromuscular tears are frequently difficult to recognize.

Physical examination may reveal the following findings:

- The presence of a central ballooning-type defect
- Descent of the area of the vaginal wall below the bladder neck
- Descent of the cervix or apical vaginal area
- The presence or absence of sulci extending lateroanteriorly, which would indicate that lateral detachment to the arcus is maintained or lost.

Anterior Vaginal Colporrhaphy

Anatomic correction of an anterior defect or cystocele will generally relieve symptoms of protrusion and pressure, and usually will improve micturition function when abnormal micturition is associated temporally with the defect and if there is no associated neuropathy. If a single, well-defined midline defect is recognized, excision of the weak vaginal wall and an imbricating closure of the defect may be performed. Most central

anterior defects require a more extensive dissection of the vesicovaginal space. Following this dissection, many surgeons then separate the vaginal mucosa and submucosal layers from the fibromuscular layer out to a point lateral to the defect, followed by midline plication of this tissue, then excision of excess epithelium, and closure. **It appears of great importance to maintain the continuum of repaired fibromuscular tissue to a well-supported vaginal apex.** A high central defect may also be corrected via a transabdominal approach by dissecting between the base of the bladder and the upper one third of the anterior vaginal wall. The defective tissue may then be wedged out and the defect closed with running or interrupted sutures. This approach may be of use when performing transabdominal procedures for apical suspension.

If the patient has significant stress incontinence (based on report or the presence of occult or potential incontinence), an appropriate bladder neck suspension may be performed simultaneously with the anterior repair (see Chapter 23). When performing midurethral sling procedures, it may be preferable not to extend the repair procedure below the urethra, but instead to make a separate incision for the sling. Maintaining some degree of the urethrovesical angle may improve the results of any incontinence procedure. If the patient has voiding dysfunction (reports of incomplete emptying and a high residual urine) and stress incontinence, appropriate urodynamic evaluation should be performed before a procedure is selected, and the patient should be made aware of the potential for continued problems after surgery.

Recurrence rates of traditional "fibromuscular plication" anterior repairs vary from 3% to 92% (47,48,49,50,51,52,53,54,55,56); however, studies define recurrence in numerous ways, from minimal prolapse to stage III descent. The clinical significance of recurrent mild cystoceles (stage I) that are asymptomatic is debatable because many of these defects do not progress to larger ones. When traditional anterior repairs are performed in patients with POP-Q stage II or greater cystoceles (frequently concurrently with other procedures), a 20% recurrence rate of stage II or greater prolapse is not uncommon, although overall recurrence rates as low as 3% have been reported (50). Many studies do not define how the subjects were evaluated postoperatively and vary with respect to patient populations, type of and severity of defects, presence of concurrent defects, surgical technique, and follow-up time and length. Some studies have suggested higher recurrence rates when these repairs are performed concurrently with sacrospinous suspensions and hypothesize that this type of apical suspension may predispose the repair anterior wall to greater pressure transmission (51,57,58). These studies may show higher failure rates because patients having such concurrent repairs may be more likely to have more complicated forms of prolapse or more extensive pelvic floor defects than other patients.

The addition of adjunctive graft materials empirically should improve success rates. Two randomized trials (55,56) suggest modest improvement in success, with an additional 12% to 18% to the "cure" rates after 1 year when polyglactin mesh (Vicryl) was placed over the midline plication compared with standard repair. However, most surgeons have abandoned this type of mesh because of subsequent failures. Other graft materials appear to have more promise. Fascial autologous grafts, allografts, xenografts, and newer synthetics are presently used by many surgeons with variable short-term success. Thus far, there are little data on adverse effects and success rates after 3 years. These materials have been used in several ways in the anterior compartment, including placement of smaller grafts to bolster suture lines and larger grafts to provide complete substitution of the entire anterior support plate from the pubis to the arcus to the vaginal apex (59,60,61,62,63,64).

Paravaginal Repair

The paravaginal or "lateral defect" repair involves reattachment of the anterior lateral vaginal sulcus to the obturator internus fascia and, in some cases, muscle at the level of the arcus tendineus pelvis ("white line") (65,66). It is usually performed as

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a bilateral procedure via transvaginal or retropubic (abdominal or laparoscopic) access. The procedure essentially restores normal anatomy; however, as it is not practical to rebuild the defective endopelvic–fascial bridge to the pelvic sidewall, it attaches the vaginal wall itself. Observational studies have reported good success with this procedure (80%–95%) (67,68,69,70,71,72); however, long-term data on durability and function are lacking. **Most women with anteriolateral detachments usually have separation of the upper vaginal fornices from the arcus tendineus immediately adjacent to the ischial spine (Fig. 24.11) (73). Thus, it is important to resuspend those specific areas.**

It is difficult to achieve optimal results when the paravaginal repair is used in combination with traditional central repairs because of the creation of tension on opposing suture lines. A repair that removes a weakened central vaginal wall may decrease the side-to-side dimensions of the anterior vaginal wall, making it difficult to suspend its lateral points more laterally. When large central defects coexist with lateral defects, one option is an extensive central repair accompanied by a good apical support procedure. This changes the shape of the vagina to a more cylindrical structure. Another choice is placement of a graft

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to span the entire anterior rhomboid-shaped plate, thus augmenting anterior paravaginal tissue strength. The graft with tension adjusted may be anchored to the arcus tendineus along with the adjacent vaginal wall from the level of the pubic rami to the ischial spine.

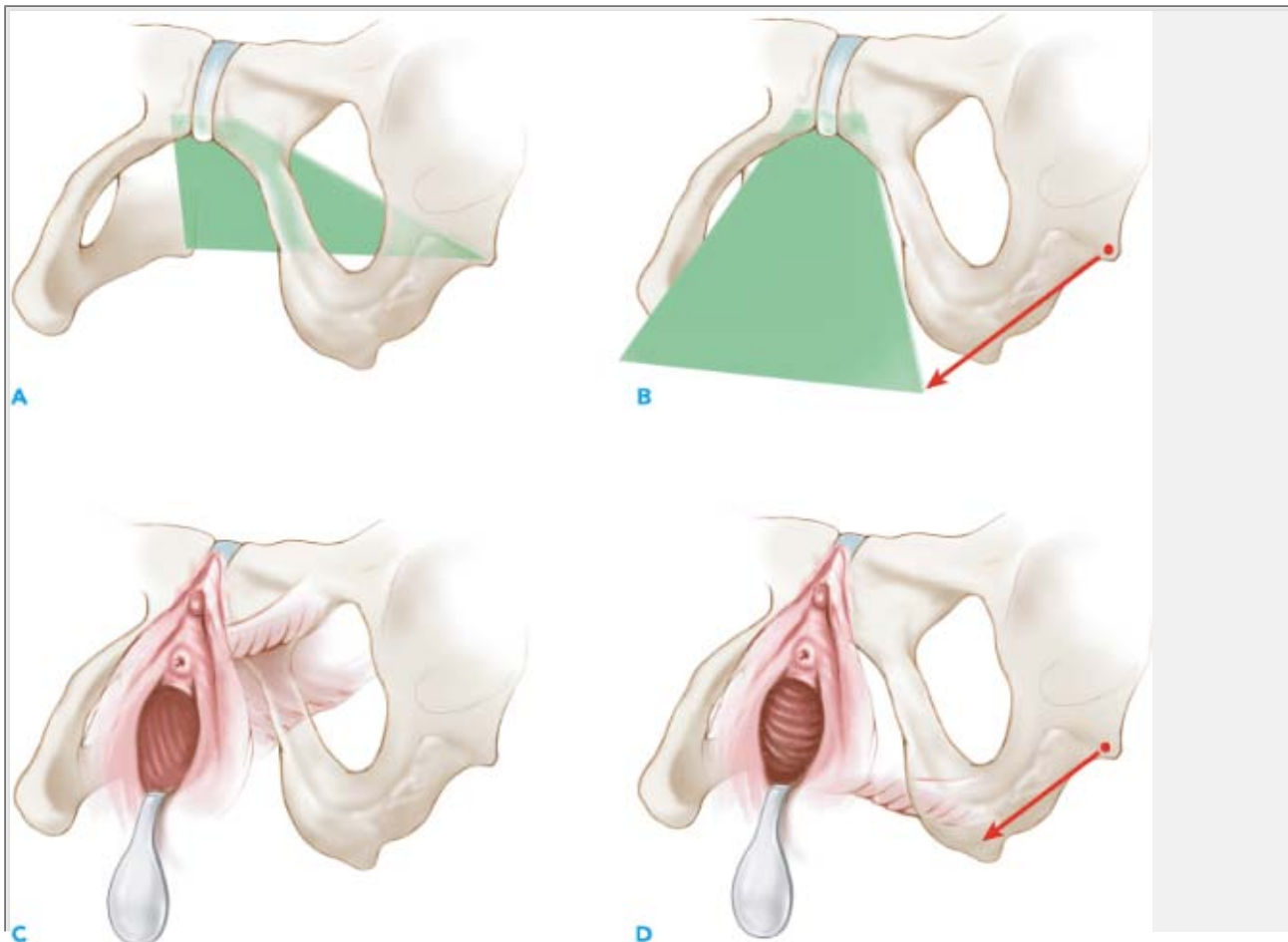


Figure 24.11 Schematics illustrating normal attachments of the anterior fibromuscular vaginal plane (A and C) and bilateral detachments of that plane from the arcus tendineus up to the level of the ischial spines (B and D). Note: For B and D to occur, there will either be concurrent apical descent or a detachment of the upper fibromuscular plane from the apical structures. (From Delancey JO. Fascial and muscular abnormalities in women with urethral hypermobility and anterior vaginal wall prolapse. *Am J Obstet Gynecol* 2002;187(1):93–98.)

Although most reports indicate that repair of anterior defects with all of these procedures relieves symptoms directly related to prolapse, there are very little data on patient satisfaction and quality-of-life improvement over time.

The Posterior Compartment

The support of the rectum and posterior vagina includes the pelvic floor musculature and connective tissue posteriorly and Denonvillier's (pararectal) fascia, which is the fibromuscular layer of the posterior vaginal wall and its lateral attachments to the lateral pelvic floor (levator) musculature and its fascia (Fig. 24.12). This lateral attachment site, the fascia levator ani, fuses with the arcus tendineus fascia pelvis at the mid- to upper level of the vagina and continues to the level of the ischial spine. Less dense, areolar, connective tissue surrounds the rectum and vagina and may supply some support to these structures as well.

Three levels of vaginal attachment have been described (74):

- Level 1 includes the upper vagina, which has cardinal/uterosacral attachments.
- Level 2 is the midvagina and its attachments laterally.
- Level 3 is the vagina between the puborectalis muscle, bulbocavernosus muscle, and perineal membrane.

The fibromuscular layer at the upper vagina fuses with the paracervical fascia and the fan-shaped cardinal ligament structure. The integrity of the attachment of this posterior vaginal layer to the anterior rectal wall just below the rectal sigmoid junction

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prevents enterocele formation. In the distal vagina, the fibromuscular layer fuses laterally with the fascia of the puborectalis and then the bulbocavernosus muscle and centrally with the perineal connective tissue. Thus, normal posterior support includes a plate of connective tissue that is attached laterally as noted, posteriorly toward sacral segments 2–4, and inferiorly to the perineum. This fibromuscular plane not only holds the rectum in place posteriorly, but also aids in preventing perineal descent by suspending the perineum to the sacrum. The constant resting tone of the pelvic floor muscles, particularly the puborectalis, serve to close the genital hiatus pulling the distal vagina and anorectal junction toward the pubic symphysis, creating an anorectal angle and a posterior deflection of the rectum, vagina, and bladder base.

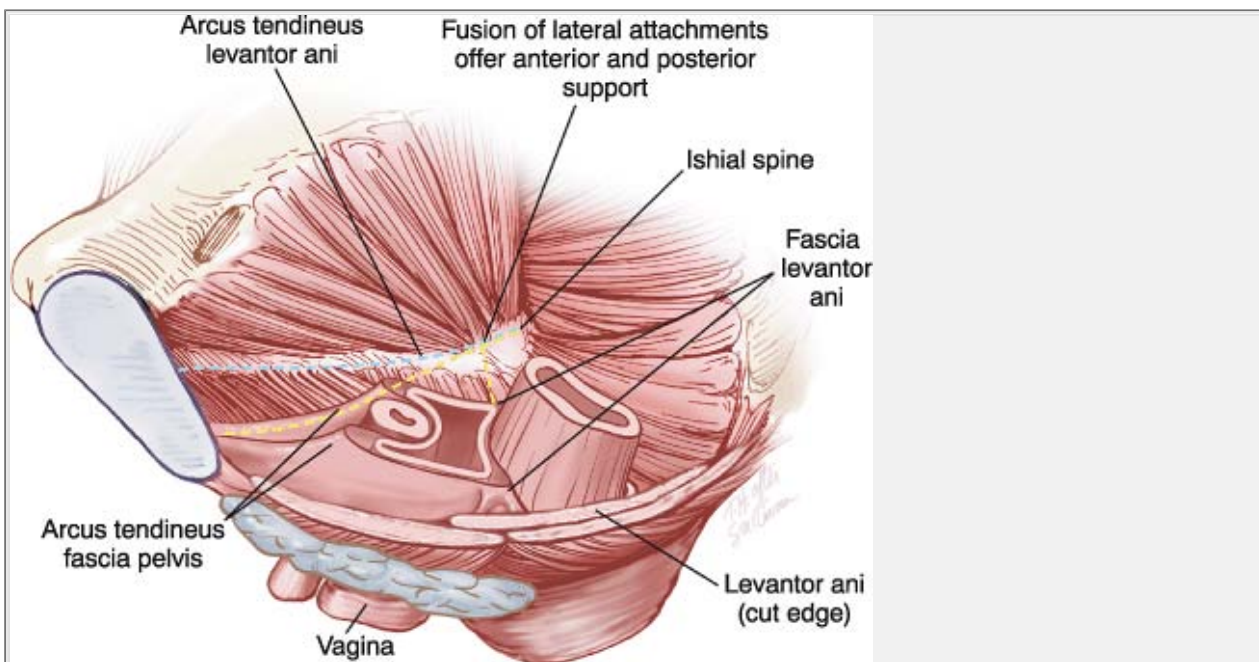


Figure 24.12 Saggital oblique view of the distal midvagina illustrating lateral connection of the posterior musculoconnective tissue wall to the fascia levator ani and anterior wall to the arcus tendineus pelvis. The attachment sites fuse together at a point closer to the ischial spine where the vagina assumes a more oval shape. (Modified by J. Taylor from illustration by Lianne Krueger Sullivan. From **Cundiff GW, Fenner D.** Evaluation and treatment of women with rectocele: focus on associated defecatory and sexual dysfunction. *Obstet Gynecol* 2004; 104:1403–1421, erratum in *Obstet Gynecol* 2005; 105:222.)

It has been hypothesized, based on careful cadaveric dissections, that most rectoceles were due to discrete tears in the Denonvillier's fascia at its lateral, apical, and perineal attachments and centrally within the fascia itself (75). Perineal detachment, along with a defect in the perineal membrane, has been described as a perineal rectocele, which is most commonly associated with reports of difficulty with defecation. Apical attachment defects are generally associated with enteroceles and occasionally sigmoidoceles.

Once a decision is made to perform surgical repair of the posterior compartment based on symptoms, type, and location of defects, an appropriate approach should be determined and the patient should be made aware of the expected outcomes and potential adverse effects such as pain and sexual dysfunction. **If the patient has defecatory dysfunction with a rectocele and symptoms of constipation, pain with defecation, fecal or flatal incontinence, or any signs of levator spasm or anal sphincter spasm, appropriate evaluation and conservative management of concurrent problems should be initiated before repair of the rectocele.** Specific types of repairs include the traditional posterior colporrhaphy, the defect-directed repair, replacement of fascia with graft materials, transanal repairs, and abdominal approaches by laparotomy or laparoscopy.

Traditional Posterior Colporrhaphy

The first description of the **posterior colporrhaphy** involved plication of the pubococcygeus muscles across the anterior rectum as well as perineal body reconstruction (76). The technique has subsequently been modified in attempts to preserve sexual function. Typically a midline incision is extended from the perineal body to the vaginal apex or to the cephalad border of a small or distal rectocele. **The Denonvillier's fascia is mobilized from the vaginal epithelium, leaving as much of this tissue as possible attached laterally to the levator fascia. After obvious defects in the rectal muscularis are repaired, the fascia**

is then plicated in the midline with interrupted or continuous sutures. The authors prefer delayed absorbable for this plication. Permanent nonbraided suture material also can be used. Braided permanent suture material is associated with a greater incidence of stitch infection and formation of granulation tissue (77). The vaginal epithelium is trimmed and closed with absorbable sutures.

When a defective perineal body or perineal membrane is present, reconstruction is performed after accompanying posterior colporrhaphy. The superficial muscles of the perineum and bulbocavernosus fascia are plicated in the midline and the skin closed as in an episiotomy repair. Detachments of the inferior portion of the Denonvillier's fascia from the perineal body are also corrected. The puborectalis muscles are plicated concurrently with these procedures by some surgeons, but this approach is associated with a high incidence of sexual dysfunction and thus is not recommended routinely. It may be worth consideration in patients who have severe prolapse accompanied by a large genital hiatus with palpable levator weakness or who are unable to contract their pelvic floor muscles. Sutures should be placed carefully through the puborectalis muscles at least 3 cm or greater posterior to their insertion on the pubic rami, thereby decreasing the tension of the plication. For those women with an enlarged hiatus and weakened puborectalis muscles

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who desire sexual function, an attempt can be made to plicate the muscles far enough posteriorly to allow two fingers to easily pass through the vaginal introitus and to reconstruct the distal posterior vagina and perineum, whereby there will not be a ledge at the site of the puborectalis plication. Outcome data on such procedures are inadequate to make conclusions regarding its efficacy; however, it is reasonable to postulate that **pelvic floor defects producing an enlarged genital hiatus are common reasons for failure of support procedures and that puborectalis plication may decrease the incidence of such failures.**

A complete review of rectocele, anorectal functional disorders, and various repairs can be found elsewhere (78). Reported anatomic cure rates for traditional posterior colporrhaphy have ranged from 76% to 90% with variable follow-up intervals (79,80,81,82,83). Most studies show a benefit in ease of defecation if patients are using splinting preoperatively; however, overall defecatory dysfunction (defined as constipation) was not relieved in most of the subjects and increased (approximately 30%) after the procedure in one study (81). These repairs appear to have little to no benefit in the treatment of fecal incontinence. It is not surprising that the repairs are not particularly effective for defecatory dysfunction related to disorders of constipation or for fecal incontinence because these problems have multifactorial causes. **De novo dyspareunia is reported to occur in 8% to 26% of sexually active patients who have traditional posterior colporrhaphy** (79,80,81,82,84) and is not always associated with levator plication procedures (85). Potential causes for dyspareunia, other than vaginal strictures or introital tightness, include scarring with immobility of the vaginal wall, levator spasm, and neuralgia associated with sutures or dissection. Dyspareunia also may occur when a Burch procedure or other procedures that displace the vaginal canal anteriorly are combined with a posterior repair (82). Careful surgical technique and appropriate choice of procedure should decrease the incidence of postoperative dyspareunia.

Defect Specific Posterior Repair

Defect or site-specific posterior repairs are restorative procedures by which posterior defects are corrected. These repairs begin with midline posterior vaginal incision through the epithelium, then continue with separation of the epithelium from the fibromuscular wall. After irrigation to provide better exposure, a finger is inserted in the rectum to help define defects

of the rectal wall and the fibromuscular layer that has been dissected from the vaginal wall submucosa. The specific defects are closed with either interrupted or running sutures (preferably the delayed absorbable type). Defect closure is accomplished in such a way to minimize tension on the surrounding tissue and may involve vertical, horizontal, or oblique approximation. When fibromuscular tissue has separated from the perineum, the upper anterior rectum, or a well-supported cervix or vaginal cuff, it is important to reapproximate these connections. Repairs of coexistent perineal and apical support defects are important. **The object of the surgery is to re-establish an intact plane of connective tissue that positions the rectum against the pelvic floor and obliterates any potential space between a well-supported cervix or vaginal cuff and the cephalad edge of the tissue plane and upper rectum.** The technique should minimize tension and potential strictures, which may be more likely to occur with traditional posterior colporrhaphy.

Initial case series reveal anatomical cure rates with mean follow-up times less than 18 months from 82% to 100% (85,86,87,88,89) and *de novo* dyspareunia rates of 2% to 7% (85), which are much lower than those seen with traditional repairs. Symptom relief appears to be as good or better than that seen with traditional repairs. The greatest concern with these and other procedures has been durability. A recent report (83) indicates that the recurrence rate of rectocele beyond the midvaginal plane was higher with defect-specific posterior repairs than with side-to-side plication procedures using laterally attached fascia pulled to the midline (33% versus 14%) and beyond the hymenal ring (11% versus 4%). The study was not randomized; however, the procedures were performed during the same period with

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consistent follow-up evaluations 1 year after surgery. Symptoms (dyspareunia, constipation, and fecal incontinence) after surgery did not differ between the two groups. Long-term follow-up of previously reported case series that had good short-term success or prospective randomized trials looking at modifications of traditional repairs versus defect-specific repairs should clearly delineate durability of these procedures.

As with anterior compartment procedures, graft materials have been used to improve the success of posterior compartment repairs. The use of a dermal allograft to augment defect-directed repairs has been described (90). The graft is sutured to the levator fascia on both sides of the defect to cover the rectovaginal plane. One concern about this technique is that, in patients with relatively thin vaginal walls, removal of the fibromuscular tissue may devascularize the mucosa and make it more subject to erosion over the graft material. The following technique may allow better healing of the vaginal epithelium anterior to the graft: **Vaginal estrogen is administered for 4 to 8 weeks preoperatively to improve the quality of vaginal mucosa in women with vaginal atrophy.** The initial surgical dissection is deep to the fibromuscular layer. Access to the lateral levator fascia is generally easily accomplished with a division of the Denonvillier's fascia at its incorporation into the posterior vaginal wall or, if the lateral attachment is not present, with combined sharp and blunt dissection to expose the paralevator fascia. This levator fascia on each side, as well as any remaining lateral Denonvillier's fascia and occasionally muscle, is incorporated into the edge of the graft with sutures. The cephalad edge of the graft is attached posteriorly to the anterior rectum at its sigmoid junction and anteriorly to a well-suspended vaginal cuff. The caudad edge is incorporated in an appropriate repair of the perineal area. With short-term, mean followup of 12 to 30 months, overall results reveal good anatomic cure rates of 89% to 100% with cadaveric dermis (90), autologous dermis (91), polyglactin mesh (56), and polypropylene mesh (92,93,94). Improvement in obstipation has also been reported. Although the numbers of subjects assessed have been relatively low, *de novo* dyspareunia rates have been between 0 and 7%, which are less than those reported for traditional posterior repairs (78).

Abdominal Approach to Posterior Repair

When abdominal sacrocolpopexy is planned for apical vaginal prolapse and concomitant rectocele is present, some have advocated extending the posterior graft down the posterior vaginal wall to correct the defect. The technique of sacral colpoperineopexy is used to replace the normal vaginal suspensory ligaments and to augment or replace the posterior fibromuscular plane with graft material that runs from the sacrum to the perineal body (95). Its purpose is to correct the posterior compartment defects and to suspend the perineal body, thus preventing descent and opening of the genital hiatus. It has been performed transabdominally or as a combined abdominal and vaginal procedure (95,96) with both Mersilene mesh and dermal allografts. Mesh erosion occurred frequently when the vagina was open: 16% for vaginal placed sutures and 40% for transvaginally placed mesh (96). The use of dermal allografts results in an anatomical cure rate of 82% with short-term follow-up and a mean of 12 months following surgery (95,96). Significant improvements also were seen in bowel symptoms. One author (97) reported results on 205 of 236 subjects who underwent an abdominal sacral colpoperineopexy with polypropylene mesh (Marlex) without opening the vagina. This procedure included two straps of mesh attached from the lateral anterior vagina to Cooper's ligament. Ten-year satisfaction rates were 68%, and erosion rates were 5%.

Laparoscopic Approach to Posterior Repair

Laparoscopic rectocele repair involves the dissection of the rectovaginal space to the perineal body with either plication of levator fascia or suturing absorbable or permanent mesh in place (98,99). A few small case series have been reported with variable results.

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Transanal Posterior Repair

The aim of transanal rectocele repair, usually performed by colorectal surgeons rather than gynecologists, is to remove or plicate redundant rectal mucosa, to decrease the size of the rectal vault, and to plicate the rectal muscularis. The rectovaginal adventitia and septum are plicated as well, probably along with the posterior vaginal muscularis. The vaginal epithelium is not incised or excised with this procedure, which probably accounts for the reported lack of adverse effects on sexual function in contrast to the vaginal approach to posterior repair. Two randomized trials (100,101) and several case series (102,103,104) from transanal repairs with mean follow-up intervals of 12 to 52 months report anatomic cure rates of 70% to 98%, improved constipation and fecal incontinence, and less need for vaginal digitation to expel stool. Complications included infections and rectovaginal fistulas, which are surprisingly rare in the reported series. From the gynecologic perspective, transanal posterior repair is an option only when the procedure is performed for defecatory dysfunction and not for prolapse of the posterior vaginal wall. The question remains whether the transanal approach with defect excision and repair improves defecatory dysfunction better than a defect-specific transperineal or transvaginal approach with imbrication of tissues to correct palpable weakness in the rectal wall and its adjacent connective tissues.

The Apical Compartment

Normal apical support includes the integrity of the cardinal/uterosacral ligaments, the upper paravaginal fibromuscular connective tissue, and, when the uterus is present, the paracervical fascia. The fibromuscular tissue of the upper vagina blends in with the paracervical fascia. Both of these are attached laterally and posterior laterally to the cardinal ligaments and uterosacral ligaments (see Fig. 24.1). The

vaginal fibromuscular tissue is also attached to the upper anterior rectum at its sigmoid junction and forms the inferior border of the cul-de-sac of Douglas. The cardinal and uterosacral ligaments are condensations of areolar connective tissue. Their origin is at the lateral borders of sacral vertebra 2–4, and they travel retroperitoneally to their insertion at the upper vagina and cervix (Fig. 24.1). They serve as the anterior and lateral borders of the cul-de-sac and cross at or just anterior to the ischial spines. The ureter is closest to the uterosacral ligament at or just posterior to its insertion on the posterior lateral cervix. If anterior cephalad traction is placed on the ureter or cervix, frequently the cardinal uterosacral ligaments will stand out as ridges lateral to the cul-de-sac; however, peritoneal folds may have similar appearance. Therefore, placement of sutures in such structures based on visual appearance alone does not always guarantee inclusion of the ligament.

Defects in apical support include:

- The loss of cardinal/uterosacral support with resultant cervical/uterine or vaginal cuff descent
- The detachment of the fibromuscular vagina from the anterior rectum with resultant enterocele or, at times, sigmoidocele into the rectovaginal space
- Tears or attenuation of the upper fibromuscular tissue, usually after hysterectomy, leading to a central apical descent that frequently presents as a ballooning defect

Often, these defects occur concurrently. Defects in cardinal/uterosacral attachment are at sites close to their insertion where breaks or tears occur; in subjects with apical descent, condensations of cardinal/uterosacral tissue can be found adjacent to the peritoneum just cephalad to the ischial spines (105).

Examination for apical defects is at times difficult. Such defects may easily be missed when large anterior or posterior defects are present. In cases when apical defects are

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suspected but not confirmed, surgeons should evaluate the apical support intraoperatively and plan for management of these defects when they are found. Traction on the cervix with a tenaculum or on the vaginal cuff both centrally and laterally with Allis clamps may reveal otherwise unrecognized defects.

Repairs of apical defects may be performed transvaginally or transabdominally, with laparotomy or laparoscopy. **Transvaginal repairs include extraperitoneal procedures such as sacrospinous suspensions, iliococcygeal suspensions, and high paravaginal suspensions** of the apical vaginal fornices to the arcus tendineus at the level of the ischial spine or to the endopelvic fascia, and intraperitoneal suspensions such as uterosacral suspensions and McCall culdoplasties (106). It is generally agreed that the vaginal apex should be resuspended in a posterior cephalad direction to a site or sites posterior and caudad to the sacral promontory. Anterior apical suspensions change the direction of the vaginal axis and may be fraught with a greater incidence of posterior compartment defects, including rectoceles, enteroceles, and sigmoidoceles.

The general principles of the repair should include management of the specific apical defects:

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If present, the attenuated part of the upper vaginal wall (fibromuscular defect) should be repaired or covered by graft material.

- The vaginal cuff or, in some instances, the cervix should be suspended without excessive tension.
- Any defect in the attachment of the upper vagina to the rectum at or below its sigmoid junction should be corrected.

Enterocoele repairs may include:

- Removal of the peritoneal sac with closure of the peritoneal defect, followed by closure of the fascial or fibromuscular defect or both below it
- Dissection and reduction of the peritoneal sac and closure of the defect
- Obliteration of the peritoneal sac from within with transabdominal Halban or Moschowitz type procedures or transvaginal McCall or Halban procedures (107).

Historically, the treatment for symptomatic uterine prolapse has been hysterectomy, which is performed vaginally or abdominally in combination with an apical suspension procedure, and repair of coexisting defects. Apical support procedures that have been described for use when the uterus or cervix is to be kept in place include Manchester and Gilliam procedures and fixation of the cervix to the sacrospinous ligament (108). The other procedures described in this section may also be used in women who desire uterine conservation. Adequate outcome data on such uterine sparing procedures are not yet available. When the cervix is absent, in addition to repair of fibromuscular defects, both fibromuscular planes anterior and posterior to the vaginal cuff should be attached to whatever suspension is employed.

Sacrospinous Ligament Fixation

The fixation of the vaginal apex to the sacrospinous ligament, the tendinous component of the coccygeus muscle, was first described in 1958 (109) and subsequently was modified in Europe and the United States (110,111,112). **Access is traditionally extraperitoneal via the rectovaginal space with penetration of the pararectal (Denonvillier's fascia) at the level of the ischial spine to expose the muscle and ligament. Variations to this approach to the**

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ligament include approaches through an anterior lateral approach, an apical approach posterior to the uterosacral ligament, and a laparoscopic approach (113,114,115). Bilateral sacrospinous ligament suspensions (116,117) have also been advocated; however, these techniques may impose a greater degree of tension on the sutures and, at times, create a band of apical vagina across the rectum at the level of the suspension. Whether this can cause defecatory dysfunction is debatable. The advantages of the sacrospinous fixation procedure include (i) its transvaginal extraperitoneal approach, (ii) resultant posterior vaginal deflection, and (iii) the fact that it is a relatively durable repair if performed correctly. Reported success for apical support has been good—approximately 97%—with follow-up times ranging from 1 month to 11 years (106). However, there have

been subsequent reports of high rates of anterior vaginal prolapse (51,57,58). It is not clear whether this observation is related to the procedure and its exaggerated posterior vaginal deflection or to other inherent factors for anterior prolapse in those women who underwent the procedures. Other disadvantages of the procedure include (i) relative difficulty in adequately exposing the ligament, (ii) an unnatural lateral vaginal deflection toward the fixation site, (iii) an inability to perform without excessive tension when the vaginal length is compromised, as may be the case in repeat procedures, (iv) potential risk for sciatic nerve or pudendal nerve or vessel injury, and (v) occasional need to shorten or narrow the upper vagina when a fibromuscular defect involves much of the apical area. Some of these problems are not unique to this procedure.

Iliococcygeal Vaginal Suspension

Iliococcygeal vaginal suspension involves the attachment, usually bilaterally, of the vaginal apex to the iliococcygeus muscle and fascia (117,118,119). Extraperitoneal access is achieved via the posterior vagina. Compared with other vaginal suspension procedures, the iliococcygeal suspension has the fewest case series in the literature (118,119,120); however, cure rates appear comparable to the sacrospinous suspension technique (106). The dissection of the area to the ischial spine is approached from a midline posterior vaginal wall incision using the ischial spine as a landmark for identifying the sacrospinous ligament and the iliococcygeal fascia anteriorly and caudad to it. A no. 1 polydioxanone suture is placed through the fascia and attached to the vaginal apex as a pulley stitch. This procedure is more easily performed bilaterally than the sacrospinous suspension and should be considered particularly in the presence of a shortened vagina. Risk of major vessel, nerve, or ureteral injury should be relatively low compared with other transvaginal suspensions.

Uterosacral Ligament Suspension

Surgical variations of the uterosacral ligament suspension originally described in 1938 (121) have been used prophylactically during hysterectomy or therapeutically for vaginal apical suspension. **A therapeutic procedure in which the vaginal apex is suspended to the uterosacral ligaments above the level of the ischial spines had excellent success rates in an observational study of 302 subjects** (122). Once access to the posterior cul-de-sac has been attained, the uterosacral ligament remnant can usually be found adjacent to the pelvic sidewall peritoneum just cephalad to the palpable ischial spine. Up to three sutures were placed in each ligament and incorporated into the anterior and posterior fibromuscular layer of the vagina. Some surgeons approximate the ligaments in the midline to close the cul-de-sac with the intention to treat or prevent enterocele formation (123). Other surgeons suspend the right and left vaginal apex to the ipsilateral uterosacral ligament, leaving the cul-de-sac open to avoid impinging on the rectum and adversely affecting bowel function.

Outcome studies have shown that recurrent apical prolapse occurs in 2% to 5% of cases within the first few years following the procedure, which is a rate comparable or superior to other transvaginal apical repairs (122,124), and the incidence of recurrent anterior defects may be less than that reported with sacrospinous suspensions. The most common serious complication has been ureteral obstruction secondary to ureteral kinking or incorporation of an ureter in a suspension stitch. This has been shown to occur

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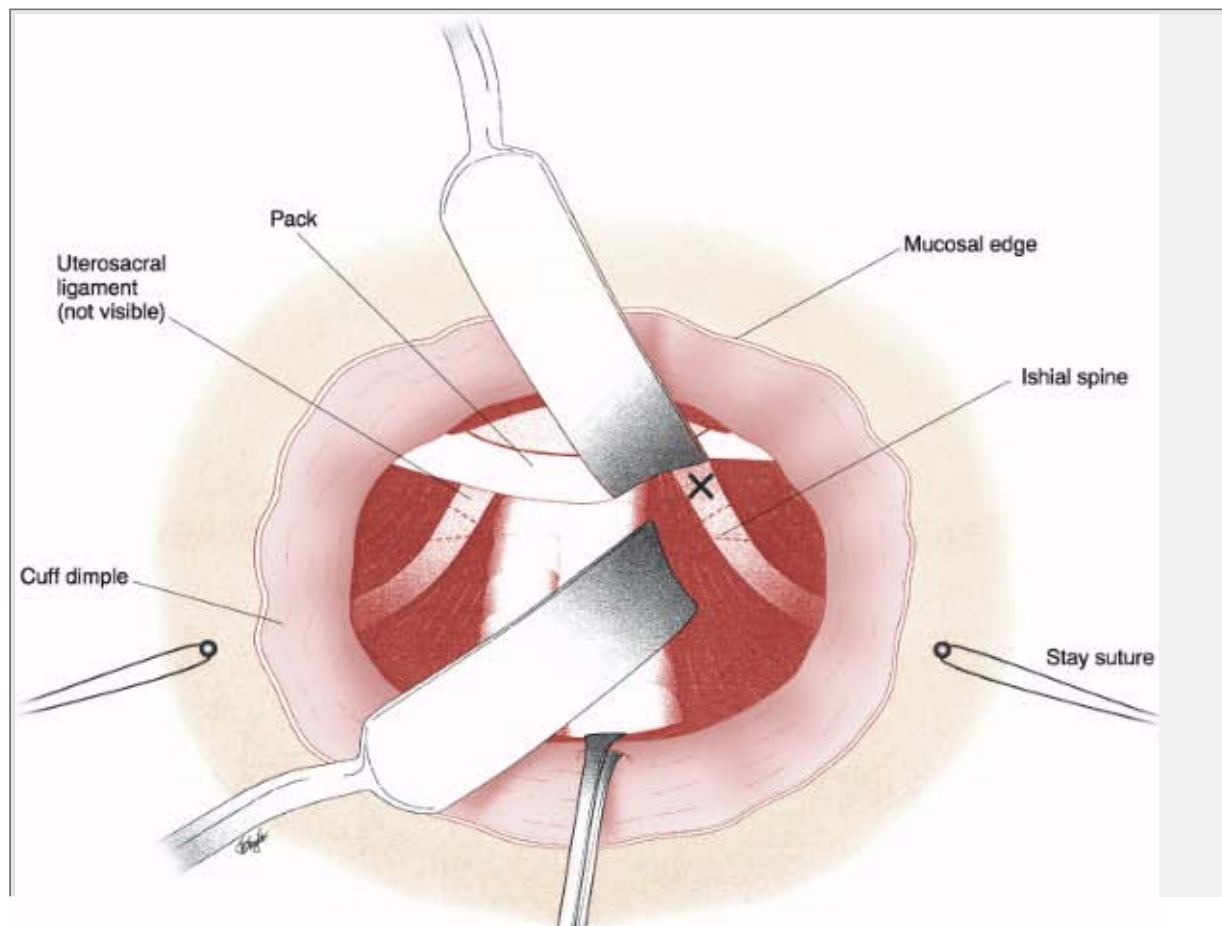
in as many as 11% of cases (124). Intraoperative cystoscopy—with documentation of ureteral patency after administration of indigo carmine dye, whereby such a problem can be corrected—is recommended.

Multiple sutures may increase the incidence of tissue devascularization and necrosis,

thus resulting in failure of the suspension. Exposure can be accomplished through the vaginal cuff after hysterectomy, a transverse incision at the vaginal cuff in cases of vaginal vault prolapse or descent, and, rarely, through a posterior colpotomy when uterine or cervical conservation is desired. When the apical vaginal wall is attenuated, it is excised. The pelvic side wall, lateral to the sigmoid colon, is exposed using Breisky–Navratil retractors and a pack to hold the small bowel cephalad and to place the sigmoid colon and side wall peritoneum on stretch (Fig. 24.13A). After palpation of the ischial spine, single permanent sutures of 0 or 1 polypropylene are placed through the peritoneum and adjacent ligament approximately 1 cm cephalad to and at the same posterior level as the ischial spines. Traction on the sutures and palpation of the site should reveal good purchase of the ligamentous structures. The sutures are tagged for use after repair of defects of the anterior compartment. The peritoneum is dissected off the vaginal fibromuscular wall posterior to the vaginal cuff. The suspension sutures are then secured with large bites into the posterior vaginal fibromuscular tissue and anterior fibromuscular tissue, then locked in place to

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approximate anterior to posterior connective tissue and to fix the suture to the vaginal apex so that it may be moved up to the ligament (Fig. 24.13B). If a rectovaginal enterocele is present, it is dissected, reduced, and closed, approximating the prerectal fascia or anterior rectal wall to the posterior fibromuscular vaginal tissue just caudad to the suspension sutures. Absorbable cuff closure sutures are placed at each cuff angle and 1 to 2 bites are taken to approximate anterior to posterior vaginal cuff over the suspension suture sites. When indicated, plication of the central cuff anterior to the posterior fibromuscular tissue with a box stitch is also performed. These sutures are secured after the suspension (pulley) sutures are tied, then cuff closure is completed from each side with the absorbable sutures in a running fashion. Cystoscopy is performed to document ureteral patency. Ureteral compromise has been noted in only 2 of 150 cases performed. The procedure provides adequate support of POP–Q point C and D in all 58 subjects evaluated more than 1 year postoperatively.



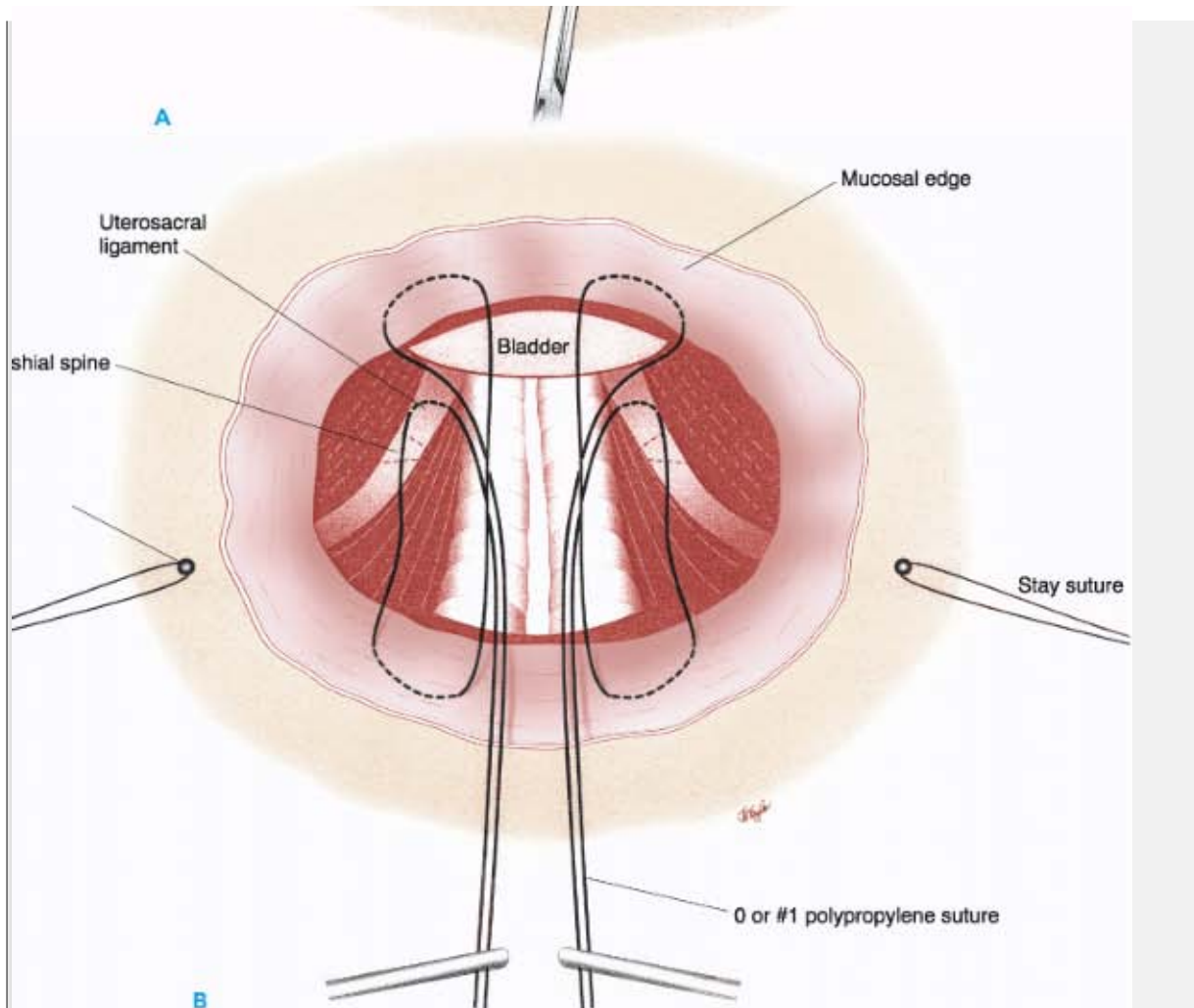


Figure 24.13 Diagrams illustrating open vaginal apical area with (A) exposure of site for suture placement or lateral pelvic side wall and (B) suture placement through ligament then through the posterior and anterior paravaginal tissue where they are locked to enable pulley action to the ligaments when tied. (Redrawn from an image by J. Taylor.)

Abdominal Procedures

Abdominal Uterosacral Suspension

Abdominal uterosacral colposuspension has been used prophylactically after hysterectomy and therapeutically for apical prolapse with cardinal/uterosacral defects. It can be performed through laparotomy incisions or by laparoscopic techniques. For the therapeutic procedure, a no. 1 polypropylene or delayed absorbable suture is placed cephalad and at the same level posterior as the ischial spines, which may be palpated transabdominally

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or with a vaginal finger to push a vaginal fornix to the spine under observation with a laparoscope. One technique is to place one or two permanent sutures through one ligament, then, after reefing across the cul-de-sac peritoneum at the sigmoid border, through the contralateral ligament, then through the fibromuscular tissue just anterior to the vaginal cuff. Tying the suture suspends the vaginal cuff and obliterates any enterocele defect. Another technique employs separate sutures placed at the same level into each uterosacral ligament and anchored anteriorly and posteriorly to the ipsilateral side of the vaginal cuff, similar to procedures performed transvaginally. Cystoscopy is performed after the procedure to

document ureteral patency.

Abdominal Sacrocolpopexy

The standard approach to transabdominal apical vaginal suspension procedures is the abdominal sacrocolpopexy. A complete review of published data on these procedures developed by the Pelvic Floor Disorders Network, which is sponsored by the National Institute of Child Health and Human Development (NICHD), has been published (125). These procedures use graft material attached to the prolapsed region of the anterior and posterior vaginal walls at or encompassing the vaginal apex and suspended to the anterior longitudinal ligament of the sacrum. Cervical sacral suspensions may also be performed when uterine or cervical conservation is desired. Surgical variations abound and include configuration of the graft on the vagina, the extent to which the anterior and posterior vagina are attached to the graft, variable graft and suture materials, presence or absence of peritoneal closure over the graft, and obliteration of the cul-de-sac for treatment or prevention of the enterocele or sigmoidocele. **A thorough preoperative evaluation to exclude more distal defects or stress incontinence, which should be repaired concurrently, and other lower urinary tract or anorectal problems, is important.**

In published reports (126,127,128,129,130,131,132,133,134,135,136), cure rates for apical prolapse range from 78% to 100% (most greater than 90%); when cure is defined as no postoperative prolapse, the range widens from 56% to 100%, although subsequent anterior or posterior vaginal prolapse has not been as consistently reported as has apical prolapse. Potential advantages of this procedure over transvaginal procedures are less paravaginal scarring and denervation than may be present with transvaginal approaches, and fixation of the entire vaginal apical area by a permanent piece of material to a stable structure (the anterior sacral ligament), which may be more durable than the transvaginal techniques that use the subject's own connective tissue.

Complications of these procedures include (i) erosions of graft material or suture material, which may be caused by graft or suture infection usually secondary to vaginal wall penetration, or performing the procedure adjacent to a vaginal incision, or securing the graft to an attenuated avascular wall with inadequate fibromuscular tissue (3.4%); (ii) significant intraoperative hemorrhage (especially in the presacral space) (4.8%); (iii) postoperative ileus, which may be secondary to the need for excessive packing of bowel or to extensive Halban or Moschowitz culdoplasty procedures (3.6%); (iv) small bowel obstruction, requiring reoperation (1.1%); (v) development of intra-abdominal adhesions with resultant pain and bowel dysfunction (unknown incidence); and (vi) wound complications, such as seromas and infections (4.6%) (125).

Several management techniques have been advocated to minimize these problems. Empiric ways to prevent graft erosions include (i) preoperative tissue optimization with vaginal administration of estrogen and treatment of vaginitis and infection of eroded areas; (ii) the use of small-gauge monofilament sutures placed in the fibromuscular tissue, thus avoiding full thickness passage; and (iii) excision of a portion of the vaginal apex when the vaginal wall is thin and depleted of its fibromuscular layer and vascularity. Graft attachment to "healthy" fibromuscular tissue rather than to thin avascular tissue should help prevent erosion. **If such excision is necessary, or if the suspension is to be performed concurrently with a hysterectomy, good approximation of the fibromuscular layers above the mucosa, thorough irrigation, prophylactic use of antibiotics, and avoidance**

of graft placement across the suture line may decrease the likelihood of graft erosion. Choice of graft material may also be important. One would expect synthetic grafts to have greater durability than tissue grafts; however, erosion rates are more serious with

the synthetic grafts. Anecdotally, some surgeons are convinced that less porous graft material, such as GORE-TEX, has a greater likelihood of becoming infected and eroding than do porous, filamentous polypropylene meshes. Numerous case series report serious episodes of hemorrhage from the presacral venous plexus (mean incidence 4.8%; range 0.18%–16.9% of sacrocolpopexies requiring, at a minimum, transfusion) (125). This problem is less likely if dissection and graft fixation is limited to the level of S1 and S2 just caudad to the promontory and with the use of good light and meticulous dissection techniques to expose the anterior sacral ligament.

Careful tissue handling and packing technique may minimize postoperative ileus and adhesions. Incorporation of the sigmoid into a closure of the cul-de-sac posterior to the graft may also slow bowel function postoperatively. Small bowel obstruction has resulted from direct adhesive processes involving grafts to small bowel. Complete extra peritonealization of the graft using flaps of peritoneum dissected from the prolapsed area and the peritoneum anterior to the sacral promontory and lateral to the right side of the sigmoid colon should prevent this complication. However, loops of bowel have been seen to prolapse through small defects in peritoneal closure with the same effect. Careful technique with adherence to basic surgical principles may help prevent this and other complications related to laparotomy.

Laparoscopic Techniques

As with most pelvic operations, sacrocolpopexy has been successfully accomplished by the laparoscopic route and has the potential to offer patients the benefits of less postoperative discomfort and faster recovery as well as potential lower risks for adhesions and ileus. Outcomes depend on the expertise and experience of the surgeon; "cutting corners" to shorten the procedure could affect anatomical success. The applicability of the procedures is limited by the need for a relatively high level of technical skill.

For sacrocolpopexy, whether through laparotomy or laparoscopy, the pelvis should be completely exposed with the lower sigmoid colon stretched cephalad (Fig. 24.14).

- With a vaginal obturator (an EEA sizer) placed vaginally to visualize the area that is not covered by the bladder or rectum, the peritoneum is dissected from the underlying vaginal fibromuscular layer anteriorly to bladder reflection and posteriorly at least to the level of the sigmoid rectal junction, creating bilateral peritoneal flaps. Laterally, vascular bundles are visible.
- Two separate loosely woven polypropylene mesh grafts are shaped similar to boat paddles. The "paddle" portions are shaped to cover the areas anterior to the apex and posterior to the apex, respectively, and the "handles," which are approximately 8 to 10 cm in length and 1 cm wide, are anchored to the anterior sacral ligament. The paddle portions are secured circumferentially to the fibromuscular layers anteriorly and posteriorly with six to eight monofilament 3-0 nylon sutures and one or two sutures placed centrally (Fig. 24.14A).
- When the fibromuscular tissue in the area is attenuated, a portion of the vaginal wall is excised and closed as noted previously.
- The peritoneum overlying sacral vertebrae 1 and 2 is incised while retracting the sigmoid colon to the left, and careful dissection is employed down to the anterior ligament. Care is taken to stay well medial to the right ureter and hypogastric vessels.

- Hemoclips are placed caudad and cephalad on the middle sacral vessels if it is felt that this will allow more optimal suture placement. The peritoneal incision is extended into the right cul-de-sac area adjacent to the sigmoid.
- Closure of the cul-de-sac lateral to the sigmoid on the left and approximation of the distal presigmoid fat to the distal edge of the posterior graft is accomplished

with box stitches of 0-delayed absorbable sutures. It is thought that these procedures and the retroperitonealization of the graft through the right side of the cul-de-sac will prevent posterior enterocele and sigmoidocele as well as a Halban or Moschowitz procedure.

- The two "handle" ends of the graft are then brought to the point of sacral attachment, where their length is adjusted to remove any tension on the vaginal sutures and secured to the anterior sacral ligament with no. 1 permanent braided nylon sutures (Fig. 24.14B).
- Reperitonealization of the graft is then performed using the right cul-de-sac peritoneum and peritoneal flaps dissected from the vaginal apical area; occasionally presigmoid fat is used,

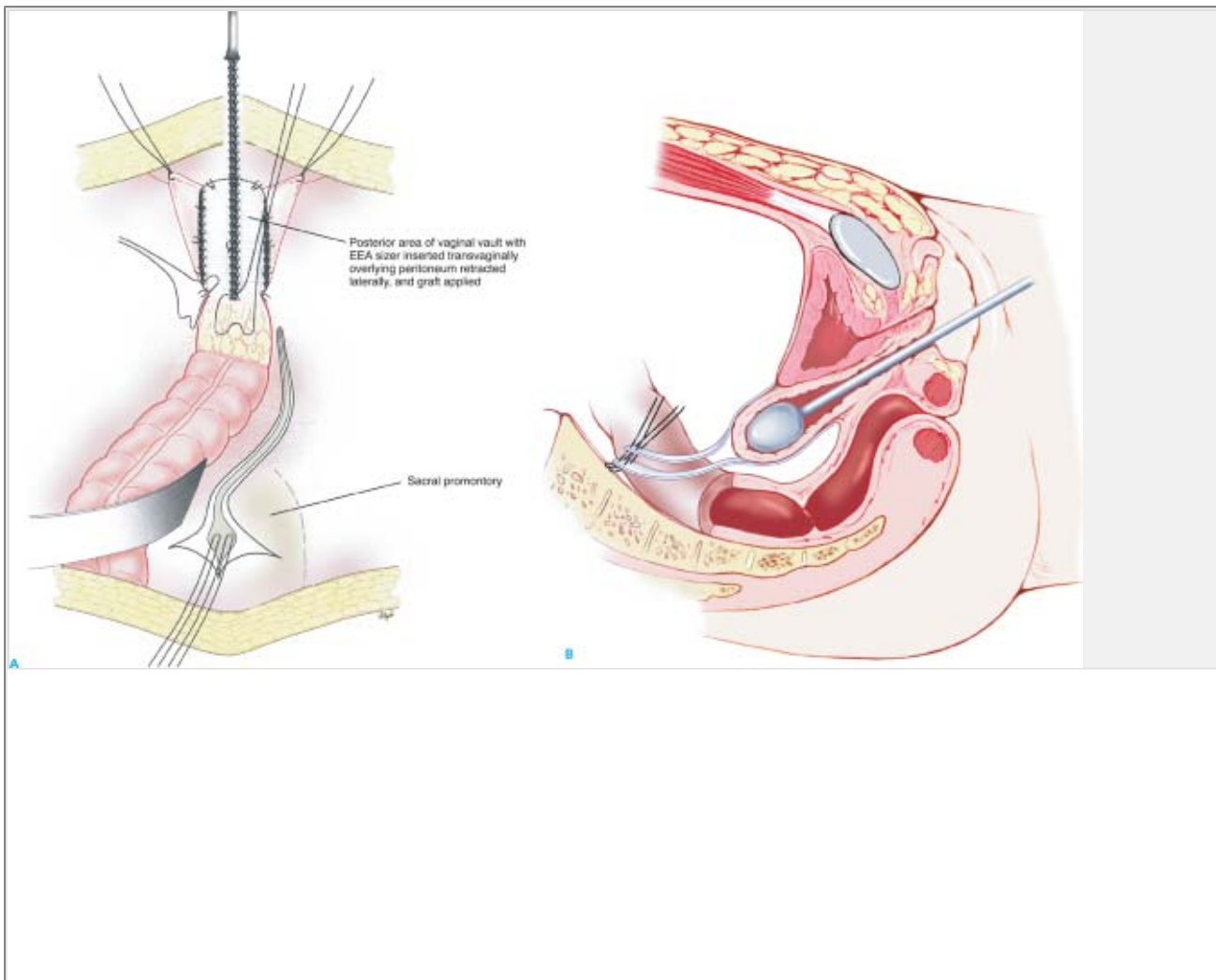


Figure 24.14 Sacrocolpopexy: (A) Illustrates (i) graft attachment to the posterior area of prolapsed vagina to or below the rectal-sigmoid junction after the overlying peritoneum has been dissected and flapped laterally and (ii) exposure of the presacral space with suture placement through the anterior sacral ligament. An appropriately shaped second graft is placed anteriorly. B: illustrates attachment of both grafts without tension to the sacrum. Prevention of subsequent enterocele and/or sigmoidocele is accomplished by box closure of the cul-de-sac peritoneum lateral to the left side of the sigmoid, attachment of the presigmoid fat to the graft centrally, and reperitonealization of the graft through the right side of the cul-de-sac. EEA, end-to-end anastomosis sizer. (Redrawn by J. Taylor.)

Following this procedure, adjunctive procedures such as paravaginal repair, Burch procedure, midurethral sling, and any transvaginal procedure that is indicated are performed. When rectocele and pelvic floor defects are present, one option is the sacral colpoperineopexy as discussed in the posterior compartment section (95). A vaginal pack is inserted for approximately 24 hours to ensure that the graft is well applied to the fibromuscular layer at points other than where sutures are placed.

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Adjunctive or Graft Materials

Graft materials have been employed in repairing defects or hernias throughout the body. The purpose of grafts is to either completely replace "weak" tissue by spanning across that tissue or to provide a scaffold for fibroblast infiltration. The patient's own connective tissue may grow into the graft, and, if the graft is degradable, replace the graft as a supportive structure. An ideal graft material should (i) be nonantigenic, (ii) exhibit a low infection rate, (iii) decrease or negate recurrence of anatomic defects, (iv) cause no harm with respect to bowel or renal function, and (v) be relatively inexpensive. Graft materials include autologous tissues, cadaveric allografts and fascia, dermis and other connective tissues, xenografts from animal sources, and various synthetic materials. Allografts and xenografts are treated with processes to remove living cells, thus negating their antigenic potential and allowing them to serve as a temporary connective tissue scaffold. It is assumed that fresh, autologous grafts work similarly; however, there may be some fibroblast survival in fresh harvested tissue. Autologous grafts have limitations in size and shape compared with tissue taken from cadaveric or animal sources. Synthetic grafts are permanent and, as long as the tissues to which they are secured retain their position and strength, they should be durable. Autografts, allografts, and xenografts depend on adequate tissue growth from the subject and potentially may have higher failure rates than synthetic ones. Synthetic grafts are more subject to erosion. Graft erosion may produce bothersome discharge, pain, and sexual dysfunction with vaginal scarring. This may be more likely to occur in women with attenuated, scarred, or less vascular tissue at the time of the repair. More loosely woven polypropylene meshes appear to exhibit fewer problems with erosion and infection than previously used synthetic graft material.

The new midurethral sling procedures that use such mesh have reported erosion rates of 1% or less as compared with rates as high as 6% with more tightly woven polypropylene and polyethylene grafts. A greater incidence of graft infection has been reported when other synthetic grafts are used. One would expect higher rates of erosion and infection when large pieces of graft material are used adjunctively to the vaginal wall; however, there have been favorable reports in which loosely woven polypropylene mesh was used in this manner. Small areas of eroded polypropylene graft may be removed with the surrounding tissue to the point where there is good tissue growth into the graft, and the defect can then be closed. Graft erosion into the bladder, urethra, or rectum is less common than in

the vagina. When erosion occurs, however, management is more difficult and long-term adverse effects more common. Numerous surgeons have been reticent to use synthetic graft materials to augment paravaginal musculoconnective tissue support because of complications from erosion. There remains a need for long-term follow-up on subjects who have repairs with graft material, not only to assess anatomical results and complications, but also to assess subsequent sexual function, presence and absence of pain, and patient satisfaction.

Vaginal Obliterative Procedures

Colpocleisis or vaginal narrowing procedures may be appropriate choices for debilitated patients who do not desire vaginal function (137,138), because complete vaginal reconstructive procedures may last several hours and are associated with potentially higher blood loss and increased morbidity. Many variations exist, from partial colpocleisis (where some portion of the vaginal epithelium is left to provide drainage tracts for cervical or upper genital discharge) to total colpectomy (where all of the vaginal epithelium is removed from the hymen posteriorly to within 0.5–2 cm of the external urethral meatus anteriorly). If hysterectomy is performed, blood loss is greater and operative time is longer than procedures without hysterectomy (139). These techniques should include a high perineorrhaphy and often a plication of the puborectalis muscles to reinforce posterior support and to reduce the genital hiatus, with the goal of decreasing the chance of recurrent prolapse. Case series have reported success rates as high as 100%, although the population of patients, by nature of their relatively short life expectancy and limited activity, are probably at lower risk for recurrence. In some instances in which most of the defects are anterior and posterior, a modified anterior and posterior colporrhaphy

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may be performed, whereby relatively large portions of the anterior and posterior vaginal wall are removed, and closed creating a narrow (1–2 cm diameter) cylindrical vagina. As with the colpocleisis, the success of the procedure is augmented by an extensive perineorrhaphy and puborectalis plication. Such a procedure may be performed quickly and with relatively low morbidity. The prevention or treatment of stress incontinence, voiding dysfunction, and colorectal dysfunction in the context of these procedures can be problematic. Careful preoperative history and evaluation, if indicated, is important so that additional conservative therapies or operative techniques such as pubourethral plications or less invasive tension-free slings may be employed.

Comparison of Abdominal versus Vaginal Approaches

In recent years there has been controversy as to whether transvaginal or transabdominal procedures for prolapse are best. One cannot discern which is optimal from reports of retrospective and prospective case series because of the considerable differences in numerous factors, including follow-up, characteristics of the subjects, definitions of success and failure, and the expertise or experience of the surgeons performing the procedures. Three prospective randomized trials have compared sacrocolpopexy and sacrospinous suspension procedures (140,141,142). All three trials showed some increased durability in the sacrocolpopexy group; however, in one of these studies the differences were not statistically significant (142). In the study in which sexual function was examined (141), there was a greater incidence of dyspareunia in the transvaginal group. Most case series reveal that the incidence of serious complications, such as small bowel obstructions, significant hemorrhage, presacral graft infections, pulmonary embolus, and short-term problems (i.e., ileus, hernias, wound seromas or infections, and longer hospitalizations), are more likely to occur in the group undergoing sacrocolpopexy. Vaginal scarring, strictures, and vaginal wall erosions or granulation tissue appear more likely in

the group undergoing transvaginal surgery. To date, there is no randomized comparison of vaginal procedures using high uterosacral suspensions and innovative repairs of the fibromuscular tissues, which are less likely to produce strictures than was the case 10 or more years ago.

Most pelvic surgeons would agree that (i) older, less healthy individuals who are more likely to have surgical and medical complications and cannot or will not tolerate a pessary would derive greater benefit from transvaginal approaches and occasionally obliterative approaches, and (ii) relatively healthy, sexually active women with relatively short vaginas and apical prolapse or with isolated apical defects would derive greater benefit from sacrocolpopexy. For the remainder of the patients with apical prolapse, with or without more distal defects, it would ideal if surgeons were equally skilled, knowledgeable, and experienced in both abdominal and vaginal approaches to provide care that is truly individualized, rather than emphasizing one approach to the exclusion of another.

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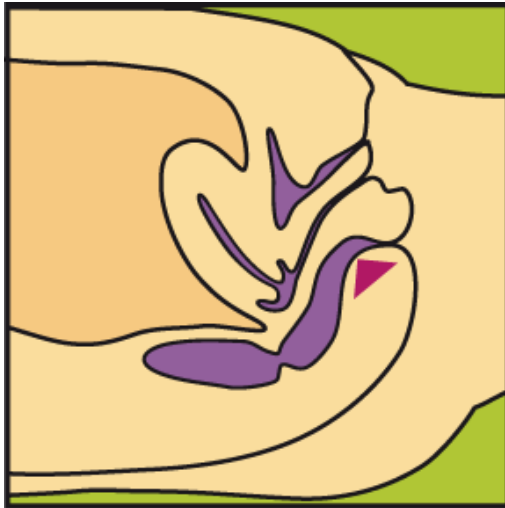
> Table of Contents > Section VI - Urogynecology and Pelvic Reconstructive Surgery > 25 - Anorectal Dysfunction

25

Anorectal Dysfunction

Robert E. Gutman

Geoffrey W. Cundiff



- **Defecatory dysfunction and fecal incontinence are common conditions that have tremendous psychosocial and economic implications.**
- **The differential diagnosis for anorectal dysfunction is broad and can be classified into systemic factors, anatomic and structural abnormalities, and functional disorders.**
- **A thorough history and physical examination is critical for the evaluation of fecal incontinence and defecatory dysfunction, as well as appropriate ancillary testing.**

Treatment of anorectal dysfunction should focus on treatment of the underlying condition with nonsurgical management attempted before surgery.

- **Overlapping sphincteroplasty is the procedure of choice for fecal incontinence caused by a disrupted anal sphincter.**

Anorectal dysfunction encompasses a variety of conditions that disrupt normal anorectal function. Such conditions can be subdivided as those that cause defecatory dysfunction and fecal incontinence. Although anorectal dysfunction transcends any individual medical specialty, the pathophysiology, evaluation, and management of conditions relevant to obstetrician–gynecologists are presented in this chapter.

Normal Colorectal Function

Anal continence and defecation are complex physiologic processes that require intact and coordinated neurologic and anatomic function, including colonic absorption and motility, rectal compliance, anorectal sensation, and the multifaceted continence mechanism. An understanding of normal physiology and pathophysiology is essential to the treatment of women with anorectal dysfunction.

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Stool Formation and Colonic Transit

The colon plays an important role in absorption and regulation of water and electrolytes. **As much as 5 liters of water and associated electrolytes can be absorbed in 1 day.** Parasympathetic–mediated peristaltic contraction of colonic smooth muscle transfers fecal material to the rectum. A delay in stool transit at the rectosigmoid region of the colon allows for maximal absorption of water and sodium.

Storage

As stool accumulates in the rectosigmoid, rectal distention triggers a transient decrease in the internal anal sphincter (IAS) tone and an increase in the external anal sphincter (EAS) tone known as the *rectoanal inhibitory reflex*. Exposure of the anal canal to fecal matter facilitates *sampling*, whereby the anal canal and its abundant sensory nerves determine stool consistency (i.e., solid, liquid, or gas). *Accommodation* occurs as the normally compliant rectal vault relaxes in response to increased volume. **This cycle, combined with increased rectal distention, stimulates an urge to defecate.** This urge can be voluntarily suppressed through cortical control, resulting in further accommodation and activation of the continence mechanism.

Continence Mechanism

Muscles

The key muscles of the continence mechanism are the puborectalis, IAS, and EAS.

The puborectalis muscle originates from the pubic rami at the level of the arcus tendineus levator ani and passes laterally to the vagina and rectum in a U-shaped configuration, creating a sling around the genital hiatus. Contraction of the puborectalis muscle narrows the genital hiatus, developing the near 90-degree anorectal angle. The resting tone of the puborectalis muscle serves as the primary continence mechanism for solid stool. The IAS and EAS are essential for continence of flatus and liquid stool. The internal sphincter maintains most of the resting tone for the sphincter complex through autonomic reflex arcs and is essential for passive continence. Although the external sphincter also maintains constant resting tone, it is ultimately responsible for preventing fecal urgency and stress incontinence associated with sudden increases in intra-abdominal pressure. This function is under both voluntary and involuntary control. The anal cushions act as the final anatomic barrier. They fill with blood, causing occlusion of the anal canal.

Nerves

Many pathologic states disrupt normal function through denervation. **The IAS receives its sympathetic supply from L5, which passes through the pelvic plexus via the hypogastric plexus.** The parasympathetic supply from S2–4 synapses at the pelvic plexus, where it joins the sympathetic nerves. The IAS acts through reflex arcs at the spinal cord without voluntary control. The puborectalis (levator ani) is innervated by branches of the S2–4 sacral roots and does not receive direct innervation from the pudendal nerve (1). The EAS is innervated bilaterally by the pudendal nerve (S2–4) via Alcock's canal. The pudendal nerve fibers cross over at the level of the spinal cord, allowing preservation of EAS function in the event of unilateral damage. The rich sensory supply from the anal canal travels along the inferior rectal branch of the pudendal nerve.

Evacuation

Initiation of defecation is normally under cortical control. As previously discussed, delivery of stool to the rectum stimulates the rectoanal inhibitory reflex, permitting sampling followed by accommodation. Further rectal distention results in an urge to defecate. Evacuation occurs with voluntary relaxation of the pelvic floor muscles (puborectalis muscle and EAS) in conjunction with increased intra-abdominal and intrarectal pressure

from Valsalva. This results in widening of the anorectal angle and shortening of the anal canal, which facilitates emptying. Coordinated peristaltic activity of the rectosigmoid assists evacuation. After this process is complete, the closing reflex is initiated, resulting in contraction of the pelvic floor muscles and activation of the continence mechanism.

Epidemiology

The epidemiology of anorectal dysfunction has been best defined in terms of the incidence and prevalence of fecal incontinence. Few studies have been done to assess the incidence and prevalence of defecatory dysfunction.

Defecatory Dysfunction

The term *defecatory dysfunction* often is used synonymously with the symptom of constipation. **Constipation is an imprecise term used by patients to report a variety of symptoms, including infrequent stools, dyschezia, straining, variation in stool consistency and caliber, incomplete emptying, bloating, and abdominal pain. The most common symptoms associated with constipation are straining and hard stools (2,3). Defecatory dysfunction is defined by many physicians as infrequent stools, typically fewer than three bowel movements per week.** This definition is based on stool frequency studies in which 95% of women have more than three bowel movements per week. Using this definition, the prevalence of constipation should be 5% (4). However, the prevalence of constipation has been estimated to range from 2% to 28%, depending on the definition applied (5,6,7).

There is an increased prevalence of constipation among women and elderly individuals, nonwhite individuals, and those with low income and low education levels (5,6,7). Based on an estimated 2.5 million visits to U.S. physicians per year for constipation (8), with an average cost of \$2,752 per patient (9), the annual cost for evaluation of constipation would be approximately \$6.9 billion. An estimated 85% of physician visits results in a prescription; thus, drug costs would increase this amount substantially (8). Constipation does have a detrimental effect on health-related quality of life (3,10). Constipation contributed to decreased mental and physical scores for quality of life on the SF-36 Health Survey in a Canadian-based population (10).

Fecal Incontinence

The reported prevalence of fecal incontinence varies between 2% and 3% for community-dwelling individuals, 3% to 17% for those of increased age, and 46% to 54% for nursing home residents (11). A prevalence of 28% has been reported among patients seeking benign gynecologic care (12). Epidemiological studies of fecal incontinence are compromised by social stigmata and the lack of a uniform definition. Definitions of fecal incontinence vary with respect to the type of material passed (solid, liquid, or gas), the frequency and duration of events (once in a lifetime to twice a week), and the impact on quality of life. Most authors agree that the true prevalence of this condition is underestimated in the current scientific literature. A large health survey in the United States found age, female sex, physical limitations, and poor general health to be independent risk factors associated with fecal incontinence (13).

Fecal incontinence has tremendous psychosocial and economic implications for individuals and society as a whole. The loss of such a basic function can be emotionally devastating, leading to poor self-esteem, depression, social isolation,

and decreased quality of life (12,14). Fecal incontinence is the second leading reason for nursing home placement in the United States, even though fewer than one third of individuals with this condition seek medical attention (12,14). The overall annual cost to treat

fecal incontinence is difficult to pinpoint, but accounts for more than \$400,000,000 per year in the cost of adult diapers alone (14).

Symptom-Based Approach to Colorectal Disorders

Several medical conditions cause defecatory dysfunction, fecal incontinence, or combined symptoms. Following is the differential diagnosis—a proposed classification system based on systemic factors, anatomic and structural abnormalities, and functional disorders.

Differential Diagnosis

Disordered Defecation

Causes of defecatory dysfunction have traditionally been divided into systemic disorders and idiopathic constipation (all nonsystemic causes). Idiopathic constipation can be subdivided into anatomic and structural abnormalities and functional disorders (Table 25.1).

Diabetes, hypothyroidism, and pregnancy are the most common endocrinologic systemic factors that cause constipation, and all have a component of decreased gastrointestinal motility and intestinal transit. In one study, gastrointestinal symptoms were present in 76% of patients with diabetes, including constipation, which occurred in 60% (15). In patients with diabetes, constipation is believed to be secondary to intestinal autonomic neuropathy, resulting in delayed or absent gastrocolic reflex and decreased bowel motility. This enteric neuropathy may also cause gastroparesis and diarrhea. Although diabetes has been classified with the endocrinologic causes, it should also be grouped with the enteric neuropathies. Pregnancy is not considered a disease state; however, there is an 11% to 38% prevalence of constipation that is believed to be due primarily to the effect of progesterone on smooth muscle (16). **The neurologic systemic factors can be divided into central and peripheral processes.** Spinal cord lesions, multiple sclerosis, and Parkinson disease affect the autonomic nervous system. Trauma to the sacral nerves often leads to severe constipation from decreased left-sided colonic motility, decreased rectal tone and sensation, and increased distention. These findings are also seen in patients with meningocele, damage to the lumbosacral spine, and pelvic floor trauma (17,18). Higher spinal cord lesions result in delayed sigmoid transit and decreased rectal compliance. In these upper motor neuron lesions, colonic reflexes are intact, and defecation can be initiated by digital stimulation of the anal canal (19,20). Individuals with multiple sclerosis can have no gastrocolic reflex, decreased colonic motility, decreased rectal compliance, and even rectosphincteric dyssynergia (21,22). Constipation worsens with the duration of illness and may be compounded by the side effects of medical therapy. Similar findings of

rectosphincteric dyssynergia and medication side effects are present with Parkinson disease.

Among the peripheral neurogenic disorders, dysfunction occurs at the level of the enteric nerves. The ultimate example of this finding is congenital aganglionosis (Hirschsprung disease). The absence of intramural ganglion cells in the submucosal and myenteric plexuses of the rectum causes loss of the rectosphincteric inhibitory reflex. Patients with this illness usually present with functional obstruction and proximal colonic dilation. In most patients, the condition is diagnosed within 6 months of age, although milder cases can be seen later in life.

Other systemic factors to consider are collagen vascular and muscle disorders. Importantly, some of the most commonly used prescription and over-the-counter medications, including aluminum antacids, beta-blockers, calcium channel blockers, anticholinergics, antidepressants, and opiates, cause defecatory dysfunction (Table 25.2). Lifestyle issues, such as

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inadequate fiber intake and insufficient fluid intake, can exert similar effects independently or in conjunction with other disorders.

Table 25.1 Causes of Defecatory Dysfunction and Fecal Incontinence

<i>Fecal Incontinence</i>	<i>Defecatory Dysfunction</i>
Systemic Factors	
<i>Metabolic/Endocrine</i>	
<ul style="list-style-type: none"> • Diabetes mellitus • Thyroid disease • Hypercalcemia • Hypokalemia 	<ul style="list-style-type: none"> • • • •
<i>Neurological</i>	
<ul style="list-style-type: none"> • Central Nervous System Multiple sclerosis, Parkinson disease, stroke, tumor, dementia • Peripheral Nervous System Hirschsprung disease, spina bifida, autonomic neuropathy, pudendal neuropathy 	<ul style="list-style-type: none"> • •
<i>Infectious</i>	
<ul style="list-style-type: none"> • Bacterial, viral, parasitic diarrhea 	
<i>Collagen Vascular/Muscle Disorder</i>	
<ul style="list-style-type: none"> • Systemic sclerosis, amyloidosis, myotonic dystrophy, dermatomyositis 	<ul style="list-style-type: none"> •
<i>Idiopathic/Autoimmune</i>	
<ul style="list-style-type: none"> • Inflammatory bowel disease • Food allergy 	
<i>Medications</i>	
<ul style="list-style-type: none"> • Prescription, over the counter 	<ul style="list-style-type: none"> •
Anatomical/Structural Abnormalities	
<i>Pelvic Outlet Obstruction</i>	

<ul style="list-style-type: none"> • Pelvic organ prolapse • Descending perineum syndrome • Anismus/rectosphincteric dyssynergia • Intussusception, rectal prolapse • Volvulus • Neoplasia • Benign strictures • Hemorrhoids 	<ul style="list-style-type: none"> • • • • • • • •
<i>Anal Sphincter Disruption/Fistula</i>	
<ul style="list-style-type: none"> • Obstetrical trauma • Surgical trauma • Anal intercourse • Injury (trauma, radiation proctitis) 	
Functional	
<i>Motility Disorders</i>	
<ul style="list-style-type: none"> • Global motility disorder • Colonic inertia/slow-transit constipation • Irritable bowel syndrome • Functional constipation • Functional diarrhea 	<ul style="list-style-type: none"> • • • • •
<i>Functional Limitations</i>	
<ul style="list-style-type: none"> • Decreased mobility • Decreased cognition 	<ul style="list-style-type: none"> • •

Table 25.2 Drugs Associated with Constipation**Over-the-Counter Medications**Antidiarrheals (*loperamide, Kaopectate*)

Antacids (with aluminum or calcium)

Iron supplements

Prescription Medications*Anticholinergics**Others*

Antidepressants

Iron

Antipsychotics

Barium sulfate

Antispasmodics

Metallic intoxication (arsenic, lead, mercury)

Antiparkinsonian drugs

Opiates

Antihypertensives

Nonsteroidal anti-inflammatory agents

Calcium channel blockers

Anticonvulsants

Beta-blockers

Vinca alkaloids

Diuretics

5-HT₃ antagonists (*ondansetron, granisetron*)

Ganglionic blockers

Structural abnormalities refer to the obstructive disorders, such as pelvic organ prolapse, perineal descent, intussusception, rectal prolapse, and tumors.

Functional disorders are those that do not have an identifiable anatomic or systemic etiology. Most functional disorders are motility disorders, such as slow-transit constipation/colonic inertia, irritable bowel syndrome (constipation predominant), and functional constipation. Patients also may have functional limitations, such as decreased mobility and cognition. It is important to understand that this classification system is somewhat arbitrary, and several of these conditions are interrelated.

Fecal Incontinence

Anal continence depends on a complex interaction of cognitive, anatomic, neurologic, and physiologic mechanisms. The continence mechanism can often compensate for a deficiency in one of these processes, but it can be overwhelmed with increased severity or decreased function over time. Systemic etiologies of fecal incontinence often are due to disease states that cause diarrhea. The rapid transport of large volumes of liquid stool to the rectum can produce urgency and incontinence even in healthy individuals (23). Fecal incontinence frequently results from infectious diarrhea caused by bacteria (e.g., *Clostridium*, *E. coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*), viruses (e.g., Rotavirus, Norwalk, human immunodeficiency virus [HIV]), and parasites (e.g., *Entamoeba*, *Giardia*, *Cryptosporidium*, *Ascaris*). Numerous medications and dietary items cause diarrhea and fecal incontinence (Table 25.3). Endocrine factors that can lead to fecal incontinence include diabetes mellitus and hyperthyroidism. With diabetes, diarrhea can develop from autonomic dysfunction, bacterial overgrowth, osmotic diarrhea with sugar substitutes, and pancreatic insufficiency. Inflammatory bowel disease is considered an idiopathic/autoimmune systemic factor. Ulcerative colitis and Crohn disease cause fecal incontinence during exacerbations with bouts of bloody diarrhea. Inflammatory bowel disease can also result in structural abnormalities, such as anal fissures, fistulas, abscesses, and operative complications that lead to fecal incontinence.

Table 25.3 Drugs and Dietary Items Associated with Diarrhea

<i>Over-the-Counter Medications</i>	
Laxatives	
Antacids (with magnesium)	
<i>Prescription Medications</i>	
Laxatives	Chemotherapy
Diuretics	<i>Colchicine</i>
Thyroid preparations	<i>Cholestyramine</i>
Cholinergics	<i>Neomycin</i>
Prostaglandins	<i>Para-aminosalicylic acid</i>
<i>Dietary Items</i>	
Dietetic foods, candy or chewing gum, and elixirs with <i>sorbitol</i> , <i>mannitol</i> , or <i>xylitol</i>	

Olestra
Caffeine
Ethanol
Monosodium glutamate

As with defecatory dysfunction, neurologic causes of fecal incontinence can be divided into central and peripheral disorders. Among the central nervous system disorders, upper motor neuron lesions above the level of the defecation center (located in the sacral cord) cause spastic bowel dysfunction. Cortical communication is disrupted, resulting in impaired cognitive control and sensory deficit. The anal sphincter is under spastic contraction, but digital stimulation can be performed to initiate reflex evacuation. **Head trauma, neoplasms, and cerebral vascular accidents that damage portions of the frontal lobe result in loss of control of both micturition and defecation.** Greater loss of inhibition is present when the lesion is located more anteriorly in the frontal lobe. Spinal cord trauma and lower motor neuron lesions above the defecation center tend to cause permanent loss of cortical control. For 2 to 4 weeks following spinal cord injury, "spinal shock" occurs, resulting in a temporary loss of reflexes below the level of the lesion, flaccid bowel function, constipation, and fecal impaction. After the initial shock, spastic paralysis ensues with hyperactive bowel function. The gastrocolic reflex, along with digital stimulation, initiates reflex evacuation in the absence of cortical inhibition. Fortunately, IAS tone is maintained despite the loss of EAS control for stress and urge situations. Both constipation and fecal incontinence can occur in these patients.

The demyelination that is seen in multiple sclerosis is randomly distributed and can occur at any level in the central nervous system. In addition to the somatic disruption that is similar to spinal cord injury, autonomic dysfunction frequently is present. **People with dementia and other degenerative disorders that cause cognitive impairment frequently have fecal incontinence caused by overflow incontinence.** Although sensory nerves are functioning properly, these individuals lack the cognitive awareness necessary to inhibit defecation until a socially acceptable time, and they develop overflow incontinence.

Lower motor neuron lesions occurring at or below the level of the defecation center in the sacral cord cause flaccid bowel dysfunction. Cortical communication is disrupted, resulting in impaired cognitive control and sensory deficit. The bowel reflexes, including the bulbocavernosus and anal reflexes, are interrupted. The anal sphincter is flaccid, and fecal retention with overflow incontinence usually occurs. Digital disimpaction and Valsalva often are required for evacuation. Digital stimulation has no effect, and medications tend to work

poorly. Examples of motor neuron lesions include tumor or trauma to the cauda equina, tabes dorsalis, spina bifida, and peripheral neuropathy.

The classic example of peripheral neuropathy is congenital aganglionosis (Hirschsprung disease), which was discussed earlier. The most common peripheral neuropathy occurs with diabetes. **Approximately 20% of individuals with diabetes have fecal incontinence**

(24). The cause tends to be multifactorial with the exact mechanism uncertain. Fecal incontinence can occur with diabetic diarrhea or years later from progressive disease. Individuals with diabetes frequently experience intestinal autonomic neuropathy, an abnormal gastrocolic reflex, and chronic constipation. The subsequent pelvic floor denervation causes fecal incontinence by sensory neuropathy, failure of the rectoanal inhibitory reflex, and sphincter dysfunction (25). Consequently, fecal incontinence from peripheral neuropathy can be the result of defective sampling, a disrupted rectoanal inhibitory reflex, or pudendal neuropathy with sphincter dysfunction. Patients may experience stress or urge incontinence as well as overflow incontinence.

Anatomic and structural causes of fecal incontinence are usually due to obstetric or surgical trauma. Damage or dysfunction of the IAS, EAS, and puborectalis can result in varying degrees of fecal incontinence. Those with impaired resting tone from a defective IAS will have passive incontinence (incontinence at rest), which is worse during sleep because of decreased EAS activity (26). An inability to respond to sudden distention and to suppress defecation is often seen with external sphincter dysfunction. External and internal sphincter dysfunction often result in incontinence of liquid stool. Incontinence of solid stool is usually seen with widening of the anorectal angle from damage to the puborectalis muscles. Damage to the anal cushions usually causes minor soiling. Other anatomic and structural abnormalities associated with fecal incontinence include obstructive disorders such as pelvic organ prolapse, descending perineum syndrome, anismus, and intussusception; fistulas from diverticulitis, inflammatory bowel disease, cancer, or surgical trauma; and decreased rectal compliance from inflammatory bowel disease, cancer, and radiation. Decreased compliance results in higher intraluminal pressures with smaller volumes of stool, poor storage capacity, urgency, and incontinence (27).

Functional disorders associated with fecal incontinence include irritable bowel syndrome (diarrhea variant), functional diarrhea, decreased mobility, and decreased cognition.

Combined Disorders of Defecation and Fecal Incontinence

Several conditions have the potential to cause both defecatory dysfunction and fecal incontinence (see Table 25.1). Most of these disorders cause combined symptoms through the development of fecal impaction followed by overflow incontinence. This situation can be seen with many of the neurological conditions, pelvic outlet obstructive disorders, functional disorders of irritable bowel syndrome, decreased mobility, and decreased cognition. The cause of these symptoms often is multifactorial.

Structural versus Functional Disorders

Disordered Defecation

Disordered defecation can result from outlet obstruction or functional motility disorders.

Outlet Obstruction

Anismus/Rectosphincteric Dyssynergia

Anismus is otherwise known as rectosphincteric dyssynergia, pelvic floor dyssynergia, spastic floor syndrome, and paradoxical puborectalis syndrome. The anorectal angle narrows as a result of paradoxical contraction of the puborectalis and external anal sphincter during defecation. Frequent symptoms

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include dyschezia, straining, hard stools, incomplete emptying, and tenesmus. A recent prospective study of 120 consecutive patients with dyssynergic defecation found a higher prevalence in women (77%) (28,29). The need for digital assistance (digital disimpaction or splinting) to evacuate the rectum occurs in up to 58% of patients. **Psychosocial factors, such as a history of sexual abuse, depression, eating disorder, obsessive-compulsive disorder, and stress, may play an important role in this disease.** In this study, 22% reported a history of sexual abuse, and 31% reported a history of physical abuse. One third believed the problem began during childhood, and 24% reported a precipitating illness or surgery was related to a particular event. Five percent of women claimed that pregnancy or childbirth was a precipitating factor. This condition also is seen in young children with constipation and dyschezia. The response to biofeedback and pelvic floor physical therapy, as well as the aforementioned patient characteristics, indicate a learned response mechanism is involved (28,29).

Pelvic Organ Prolapse

Pelvic organ prolapse bears special mention because it is often seen by gynecologists but inconsistently associated with defecatory dysfunction. Prolapse is very common, although many women with this condition are asymptomatic. Those with symptoms may report incomplete evacuation and the need to apply digital pressure to the posterior vaginal wall or perineum to aid in evacuation of stool (digitation or splinting). It is important to rule out other causes of constipation, because these symptoms are nonspecific, and rectocele can result from chronic straining and increased intra-abdominal pressure. **Defecatory dysfunction related to pelvic organ prolapse can result from rectocele, enterocele, or perineal descent, either individually or in combination.**

Rectocele is a herniation of the rectal mucosa through a defect in the rectovaginal septum. These site-specific defects can be transverse or longitudinal through the inferior, middle, or superior regions of the rectovaginal septum (30). **Enterocele is a herniation of a peritoneal sac and bowel through the pelvic floor, typically between the uterus or vaginal cuff and rectum. It is more common following hysterectomy and retropubic urethropexy.** There are two theories surrounding the formation of an enterocele. The first theory implicates a defect in the fibromuscular endopelvic fascia of the vagina, allowing peritoneum and bowel to herniate. The second theory attributes its formation to a support defect with full thickness protrusion, including endopelvic fascia (31). Ultimately,

the mechanism might be attributed to a combination of the two theories because some support defects are secondary to superior breaks in the rectovaginal and pubocervical fascia. **Patients with rectocele and enterocele may have similar symptoms, including pelvic pain, pressure, vaginal protrusion, obstipation, fecal incontinence and sexual dysfunction.** Although associations have been made between defecatory dysfunction and advanced stages of pelvic organ prolapse, a causal relationship remains to be established. Controversy remains as to whether anatomic herniation is the cause of these symptoms or the effect of underlying colonic dysfunction, chronic constipation, and straining.

Descending perineum syndrome is defined as descent of the perineum (at the level of the anal verge) beyond the ischial tuberosities during Valsalva. Excessive perineal descent was first described in the colorectal literature by Parks et al. in 1966 (32,33). It occurs as a result of inferior detachment of the rectovaginal septum from the perineal body. As the condition progresses, the patient can develop pudendal neuropathy from stretch injury. Perineal descent has been associated with a variety of defecatory disorders, including constipation, fecal incontinence, rectal pain, solitary rectal ulcer syndrome, rectocele, and enterocele (34).

Rectal Intussusception

Rectal intussusception or intrarectal prolapse is the circumferential prolapse of the upper rectal wall into the rectal ampulla but not through the anal verge. It occurs most often in women in the fourth and fifth decade. The most common symptoms are obstructive, including incomplete emptying, manual disimpaction,

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splinting, pain with defecation, and bleeding. Other symptoms include fecal incontinence, decreased urge to defecate, inability to distinguish between gas and feces, and mucus discharge with pruritus ani. Bleeding often originates from a solitary rectal ulcer or localized proctitis of the involved bowel segment (35). **Intussusception is frequently seen in as many as one third of women with defecatory dysfunction and other symptoms, such as constipation, rectal pain, and fecal incontinence** (36). It has also been seen in 29% of asymptomatic patients (37). The intussusception rarely develops into total rectal prolapse (38).

Functional Motility Disorders

Colonic Inertia/Slow-Transit Constipation

Severe constipation, defined as fewer than three stools per week and refractory to therapy, is relatively rare; however, these patients frequently suffer from motility disorders such as *global motility disorder* and *colonic inertia*. Women are more likely to be affected than men. Colonic inertia or slow-transit constipation is defined as the delayed passage of radiopaque markers through the proximal colon without retropulsion of markers from the left colon and in the absence of systemic or obstructive disorders. The cause remains unclear. Patients with this disorder have impaired phasic colonic motor activity

and diminished gastrocolic reflexes (39,40). Studies on the role of laxatives, absorption, hormones, psychological abnormalities, and endogenous opioids have been inconclusive. Current literature suggests a possible neurologic or smooth muscle disorder (40,41).

Functional Bowel Disorders

Functional bowel disorders, as defined by the Rome II Criteria (42), consist of irritable bowel syndrome, functional abdominal bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorders. In this section we will focus primarily on IBS.

Irritable bowel syndrome (IBS) has been estimated to have a prevalence of 10% to 20% and is more common in women and younger individuals. It accounts for 25% to 50% of all referrals to gastrointestinal clinics. Irritable bowel syndrome has distinct diagnostic criteria, including the exclusion of structural or metabolic abnormalities. **These patients often have other gastrointestinal, genitourinary, and psychological illness, including gastroesophageal reflux disease, fibromyalgia, headache, backache, chronic pelvic pain, sexual dysfunction, lower urinary tract dysfunction, depression, and anxiety.** Stressful life events seem to correlate with the onset and exacerbation of symptoms. A detailed history frequently reveals past physical or sexual abuse (42). Currently, specific criteria allow for classification of IBS into diarrhea-, constipation-, and pain-predominant categories (Table 25.4). The constipation variant is most commonly associated with defecatory dysfunction, whereas the diarrhea variant causes fecal incontinence. The pain or spastic variant causes predominantly abdominal discomfort but can also be associated with both defecatory dysfunction and fecal incontinence. After excluding organic disease, the criteria listed in Table 25.4 have a sensitivity of 65%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 76% (43).

Functional constipation *is a term created by the Rome II criteria as a unifying definition of constipation* (Table 25.5). The rationale for the criteria listed in Table 25.5 stems from the variability in patient definitions of constipation (42).

Fecal Incontinence

Sphincter Disruption

In young women, obstetric injury is the most common cause of fecal incontinence.

The mechanism of injury can be from anatomic disruption of the anal sphincter complex, pelvic floor denervation, or a combination of the two conditions. The risk factors for anal

sphincter laceration are primiparity, high birth weight, forceps delivery, and episiotomy (44,45,46). Although there are limited long-term prospective studies demonstrating the natural history of anal sphincter injury, pelvic floor neuropathy, and the progression of these conditions to fecal incontinence, current literature supports the relationship of early-onset symptoms to sphincter damage and delayed-onset symptoms to neuropathy (47).

This relationship would account for the large discrepancy in the prevalence of fecal incontinence between younger men and women that decreases as the population ages (48).

Table 25.4 Diagnostic Criteria of Irritable Bowel Syndrome^a

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features:

1. Relieved with defecation and/or
2. Onset associated with a change in frequency of stool and/or
3. Onset associated with a change in form (appearance) of stool

Supporting symptoms of IBS

1. Fewer than three bowel movements a week
2. More than three bowel movements a day
3. Hard or lumpy stools
4. Loose (mushy) or watery stools
5. Straining during a bowel movement
6. Urgency (having to rush to have a bowel movement)
7. Feeling of incomplete bowel movement
8. Abdominal fullness, bloating, or swelling

Diarrhea-predominant 1 or more of 2, 4, or 6 and none of 1, 3, or 5; or 2 or more of 2, 4, or 6 and one of 1 or 5.

Constipation-predominant 1 or more of 1, 3, or 5 and none of 2, 4, or 6; or 2 or more of 1, 3, or 5 and one of 2, 4, or 6.

IBS, irritable bowel syndrome.

^a From **Thompson WG, Longstreth GF, Drossman DA, et al.** Functional bowel disorders and functional abdominal pain. In: **Drossman DA, Corazziari E, Talley NJ, et al. eds.** *Rome II: the functional gastrointestinal disorders*. 2nd ed. McLean, VA: Degnon Associates, 2000: 351-432.

Table 25.5 Diagnostic Criteria of Functional Constipation^a

At least 12 weeks, which need not be consecutive, in the preceding 12 months of two or more of:

1. Straining >1/4 of defecations
2. Lumpy or hard stools >1/4 of defecations
3. Sensation of incomplete evacuation >1/4 of defecations
4. Sensation of anorectal obstruction/blockage >1/4 of defecations
5. Manual maneuvers to facilitate >1/4 of defecations (e.g., digital evacuation, support of the pelvic floor)
6. <3 defecations per week

If loose stools are not present, and there are insufficient criteria for IBS.

IBS, irritable bowel syndrome.

^a From **Thompson WG, Longstreth GF, Drossman DA, et al.** Functional bowel disorders and functional abdominal pain. In: **Drossman DA, Corazziari E, Talley NJ, et al. eds.** *Rome II: the functional gastrointestinal disorders*. 2nd ed. McLean, VA: Degnon Associates, 2000: 351–432.

Obstetric Trauma

Third- and fourth-degree lacerations at delivery are associated with an increased risk of fecal incontinence (odds ratio [OR] 3.09) (47). Whereas the incidence of clinically documented third- and fourth-degree anal sphincter tears is between 0.5% and 5.9% (44,46,49), occult third- and fourth-degree defects are present in 28% to 35% of primiparous women and 44% of multiparous women, and approximately one third of these patients have symptoms of anal incontinence. **Patients with occult anal sphincter tears are 8.8 times more likely to have fecal incontinence** (46,50). Forceps-assisted vaginal delivery significantly increases this risk, but the data on vacuum-assisted delivery are less conclusive (45,51,52). Elective cesarean delivery, in contrast with emergency cesarean delivery, was believed to prevent anal incontinence, but recent studies argue against any protective effect with cesarean delivery, irrespective of timing (46,51,53). **Midline episiotomy is strongly linked to sphincter damage and fecal incontinence** (45,54). One study of a large population found conflicting results, with an overall protective effect seen with episiotomy (OR 0.89). The likelihood of fourth-degree laceration was increased (OR 1.12) and of third-degree laceration was decreased (OR 0.81) (44). A Cochrane review supports the restrictive use of both midline and mediolateral episiotomy (55). In another study, an important finding was that one half of patients who underwent immediate repair of a third-degree laceration had symptoms of anal incontinence, and 85% had persistent sphincter defects on endoanal ultrasonography (56).

Surgical Trauma

Iatrogenic injury follows obstetric trauma as the second most common cause of direct sphincter damage. Surgical procedures that have been associated with fecal incontinence include anal fistula repair, anal sphincterotomy, hemorrhoidectomy, and anal dilation. Fistulotomy is the most common procedure that results in fecal incontinence. Rectovaginal or anovaginal fistulas can develop after obstetric injury, operative complications during pelvic surgery, and inflammatory bowel disease exacerbations. Fistulas cause fecal incontinence, and the degree of postoperative dysfunction depends on the location of the fistula and the amount of sphincter that is disrupted during the surgical repair. It also depends on the preoperative level of sphincter function and pudendal nerve function. Anal sphincterotomy to treat painful anal fissures can lead to incontinence by disruption of rectal sensory innervation and anal cushions and transection of the anal sphincter (57,58). Hemorrhoidectomy often results in minor soiling as a result of resection of the anal cushions, which act as the final mucosal barrier. Similar to sphincterotomy, rectal sensory innervation can be disrupted, and injury to

Sphincter Denervation

Idiopathic (primary neurogenic) fecal incontinence results from denervation of both the anal sphincter and pelvic floor muscles. Denervation injury related to obstetric trauma accounts for approximately three out of every four cases of idiopathic fecal incontinence and is the most common overall cause of fecal incontinence (60,61).

Obstetric Trauma

The two proposed mechanisms of pudendal neuropathy are stretch injury during the second stage of labor and compression of the nerve as it exits Alcock's canal (60). **Established risk factors for pelvic floor neuropathy include multiparity, high birth weight, forceps delivery, prolonged active second stage, and third-degree laceration** (62,63).

Several studies have shown increased pudendal nerve terminal motor latencies following vaginal delivery, especially after sphincter laceration (46,61,64). Most women will recover function within a few months postpartum. Others will have evidence of injury several years later, which may represent the cumulative effects of subsequent deliveries (61,65). However, fecal incontinence will develop in only a fraction of patients with neuropathy (63).

Descending Perineum Syndrome

As noted previously, prolonged straining for any reason can cause descending perineum syndrome. This syndrome is defined as descent of the perineum beyond the ischial tuberosities during Valsalva (32,33). Pudendal

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neuropathy results from stretching and entrapment of the pudendal nerve. This diagnosis is supported by findings of elongation of the pudendal nerve, prolonged pudendal nerve motor terminal latency, and decreased anal sensation in women with perineal descent (66,67,68). As pudendal neuropathy progresses, it ultimately leads to fecal incontinence (34,69).

Table 25.6 Diagnostic Criteria of Functional Diarrhea^a

At least 12 weeks, which need not be consecutive, in the preceding 12 months of:

1. Loose (mushy) or watery stools
2. Present more than 3/4 of the time; and
3. No abdominal pain

From **Thompson WG, Longstreth GF, Drossman DA, et al.** Functional Bowel disorders and functional abdominal pain. In: **Drossman DA, Corazziari E, Talley NJ, et al. eds. Rome II: The Functional Gastrointestinal Disorders.** 2nd ed. McLean, VA: Degnon Associates, 2000: 351–432.

Functional Bowel Disorders

Irritable Bowel Syndrome

The diarrhea variant of irritable bowel syndrome is often associated with fecal incontinence as well as disordered defecation. The criteria for diagnosis are in Table 25.4.

Functional Diarrhea

The Rome II criteria create a unifying definition of diarrhea called functional diarrhea (Table 25.6). The rationale for the criteria listed in Table 25.6 stems from the variability in patients' descriptions of diarrhea (42).

Pitfalls for the Pelvic Floor Surgeon

It sometimes is easy to overlook or misinterpret signs and symptoms of constipation and defecatory dysfunction. Any acute change in bowel habits must be evaluated thoroughly, and malignancy must be considered in the differential diagnosis. Even in the presence of chronic disease, malignancy must still be excluded. Persistent symptoms after an empiric trial of medical therapy should prompt further evaluation, such as a colonoscopy or flexible sigmoidoscopy. It is also possible to mistakenly attribute symptoms of defecatory dysfunction and constipation to pelvic organ prolapse when prolapse is actually the result of an underlying bowel disorder. In this case, surgical treatment of prolapse will have little lasting benefit if the underlying bowel disorder remains untreated.

History and Physical Examination

History

A thorough history and physical examination are critical to the evaluation of fecal incontinence and defecatory dysfunction. The history of present illness should focus on the bowel habits, including frequency and consistency of bowel movements (hard versus soft, formed versus unformed, diarrhea versus constipation). The duration and severity of symptoms as well as exacerbating factors are important to understanding the impact on quality of life. Patients should be questioned about straining with bowel movements, symptoms of incomplete emptying, and splinting of the perianal region, perineal body, or posterior vaginal wall to assist with evacuation. They should also be asked about the need to perform digital disimpaction because they are unlikely to volunteer this information. With respect to fecal incontinence, information should be obtained about leakage with solids, liquid, and flatus and the ability to discriminate between these different types of stool (sampling). Similar to urinary incontinence, fecal incontinence can

be stress related, urge related, or unconscious. Questions about alternating diarrhea and constipation, mucus or blood in the stools, constitutional symptoms, and changes in stool caliber can help the investigator uncover systemic and functional etiologies. Finally, it is important to ask about adaptive behaviors, pad or diaper use, and past and present treatments including surgery, physical therapy, and medications.

A large amount of information can be obtained efficiently through questionnaires. Validated questionnaires quantify symptoms, which are subjective in nature, to objectively measure response to treatment. **A valuable survey to assess defecatory dysfunction is the Colorectal–Anal Distress Inventory (CRADI), which has been incorporated into the Pelvic Floor Distress Inventory (PFDI)** (70). The latter is a useful tool for evaluating symptoms of prolapse, urinary incontinence, fecal incontinence, voiding dysfunction, and defecatory dysfunction. Other useful symptom scales and bother scores for fecal incontinence include the Wexner Score (71), Fecal Incontinence Severity Index (72), and Fecal Incontinence Quality of Life Scale (73).

The medical history, surgical history, family history, and review of systems should focus on uncovering potential systemic and obstructive disorders shown in Table 25.1. **A complete obstetric history should include the number of vaginal deliveries, operative vaginal deliveries, or presence of a third- or fourth-degree laceration, which is critical for patients with fecal incontinence.** Length of the second stage of labor, birth weight, and the use of episiotomy should be ascertained because they may pose risk factors for sphincter damage and denervation. The sexual history should include questions about prior rape, anal intercourse, and dyspareunia. Use of over-the-counter, prescription, and illegal drugs should be recorded as well as food allergies.

Physical Examination

The evaluation of anorectal dysfunction requires a basic general examination as well as a focused abdominal and pelvic examination. The general physical survey should include a global assessment of mobility and cognitive function. Routine examination of the abdomen involves inspection, palpation, and auscultation to rule out the presence of masses, organomegaly, and areas of peritoneal irritation. This examination should be followed by a detailed evaluation of the vagina, perineum, and anorectum. The goals of the pelvic examination are to define objectively the degree of prolapse and determine the integrity of the connective tissue, neurologic function, and muscular support of the pelvic organs.

Neurologic Examination

Important elements of the neurologic examination are assessment of cranial nerve function, sensation and strength of the lower extremities, and reflexes for the lower extremities, bulbocavernosus, and anal wink. These examinations evaluate the function of the lower lumbar and sacral nerve roots, recognizing the importance of the second through fourth sacral nerve roots in pelvic floor dysfunction. The perineal reflexes can

be elicited by stroking the labia majora and perianal skin or tapping the clitoris with a cotton-tipped swab. The anal wink, bulbocavernosus, and cough reflexes all test the integrity of motor innervation to the external anal sphincter (S2–4). Sensation over the inner thigh, vulva, and perirectal areas should be tested for symmetry to light touch and pinprick.

Muscle Strength

The integrity of the pelvic floor muscles should be assessed at rest and with voluntary contraction to determine strength, duration, and anterior lift. The ability to relax these muscles and tenderness on palpation should also be evaluated.

Several standardized systems have been described to objectively measure muscle strength, but none has been accepted as a standard. The puborectalis muscle should be readily palpable posteriorly as it creates a 90-degree angle between the anal and rectal canals. Voluntary contraction of this muscle "lifts" the examining finger anteriorly toward the pubic rami. An intact

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external anal sphincter muscle that has decreased tone and contractility often indicates pudendal neuropathy. Similarly, neuropathy affecting the puborectalis can be recognized by an obtuse anorectal angle and weak voluntary contraction. Similar to the urethral axis, the anorectal angle can also be tested using a cotton-tipped swab, although this test is rarely performed. Deflection is measured in the supine position at rest, with strain, and with squeeze.

Vaginal Support

The salient points of pelvic organ prolapse (see Chapter 24) for patients with defecatory dysfunction are the support of the vaginal apex, posterior wall, and perineal body, although some experts believe anterior wall defects can also affect defecatory dysfunction. The posterior wall is assessed while supporting the vaginal apex and anterior wall with a Sims' speculum. This permits the examiner to focus on identifying specific locations of rectovaginal fascial defects. A rectovaginal examination aids in identification of defects in the rectovaginal fascia or perineal body. Loss of vaginal rugation has also been reported overlying the site of a rectovaginal fascial tear (74). This technique is especially useful for enteroceles, which have a smooth, thin epithelium over the enterocele sac or peritoneum.

Normally, the perineum should be located at the level of the ischial tuberosities, or within 2 cm of this landmark. A perineum below this level, either at rest or with straining, represents perineal descent. Subjective findings of perineal descent include widening of the genital hiatus and perineal body, as well as flattening of the intergluteal sulcus. Women with perineal descent also tend to have less severe stages of pelvic organ prolapse based on the Pelvic **Organ Prolapse Quantification (POP-Q) staging system** (75) because it measures descent from the hymenal ring. Consequently, an increase in the length of the perineal body and genital hiatus with straining suggests perineal descent. The degree of perineal descent can also be measured objectively with a St. Mark's perineometer, although a thin ruler placed in the posterior introitus at the level of the ischial tuberosities also can be used. Descent is measured

as the distance the perineal body moves when the patient strains. Although pelvic floor fluoroscopy is the standard technique for measuring perineal descent, this technique is most useful in patients with symptoms of severe defecatory dysfunction and evidence of perineal descent on pelvic examination.

Anorectal Examination

Visual and digital inspection of the vagina and anus will help to identify structural abnormalities such as prolapse, fistulas, fissures, hemorrhoids, or prior trauma. As previously mentioned, a rectovaginal examination provides useful information regarding the integrity of the rectovaginal septum and can demonstrate laxity in the support of the perineal body. The rectovaginal examination also is helpful in the diagnosis of enteroceles, which can be felt as protrusion of bowel between the vaginal and rectal fingers with straining. Digital rectal examination should be performed at rest, with squeeze, and while straining. The presence of fecal material in the anal canal may suggest fecal impaction or neuromuscular weakness of the anal continence mechanism. Circumferential protrusion of the upper rectum around the examining finger during straining suggests intussusception, which often occurs in combination with laxity of the posterior rectal support along the sacrum.

The integrity of the external anal sphincter and puborectalis muscle can be evaluated by observation and palpation of these structures during voluntary contraction. Evidence of dovetailing of the perianal skin folds and the presence of a perineal scar with an asymmetric contraction often indicates a sphincter defect. When a patient is asked to contract her pelvic floor muscles, two motions should be present: The external anal sphincter should contract concentrically, and the anal verge should be pulled inward. These actions should also be apparent on digital rectal examination. As mentioned previously, the 90-degree angle created by the puborectalis should be readily palpable posteriorly and, with voluntary contraction, the examining finger should be lifted anteriorly toward the pubic rami.

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Both the puborectalis and external anal sphincter should relax during Valsalva effort. Patients with anismus may experience a paradoxical contraction of these muscles during straining. Finally, defects in the anterior aspects of the external anal sphincter may be detected by digital examination.

Testing

Sophisticated diagnostic testing is currently being used in clinical research and in anorectal physiology laboratories to quantify the function of the colon and anorectum. Following is a description of these techniques as they relate to the management of fecal incontinence and disordered defecation.

Fecal Incontinence

Endoanal Ultrasonography

Endoanal ultrasonography permits accurate imaging of both the internal and external anal sphincters. It can assess the continuity and thickness of the muscle and currently is considered the single best method for detecting anal sphincter defects.

Endoanal ultrasonography is performed using a Bruel-Kjaer (Copenhagen, Denmark) ultrasound scanner with a 360-degree rectal endoprobe (type 1850) with a 7.0 MHz transducer (focal length, 2–5 cm) housed within a plastic cone (Fig. 25.1). The normal IAS is a continuous hypoechoic band of smooth muscle surrounded by the thick echogenic layer of the striated EAS. A sphincter defect occurs when there is disruption in these muscle bands. Location and severity of the defect can be described by circumferential distance in degrees, percent thickness, and distance from the anal verge (Fig. 25.2). Measurements are usually taken in the proximal, middle, and distal anal canal. It is important to recognize the physiologic split in the proximal EAS as it merges with the puborectalis muscle of the levator ani. Misinterpretation of this finding as a sphincter defect can result in an increased prevalence of reported defects. The puborectalis muscle appears as a U-shaped or V-shaped thick echogenic layer outside the IAS in the proximal anal canal. Magnetic resonance imaging (MRI) may be equally as effective or better at diagnosing sphincter defects, especially with the use of a vaginal or rectal coil. For this purpose, MRI is more expensive, and currently its use is largely investigational. It may be beneficial in cases in which endoanal ultrasonography results are inconclusive or the quality of the study is poor.

Electromyography

Electromyography (EMG) is used to evaluate neuromuscular integrity of the EAS following a traumatic injury such as childbirth, as well as to document the presence

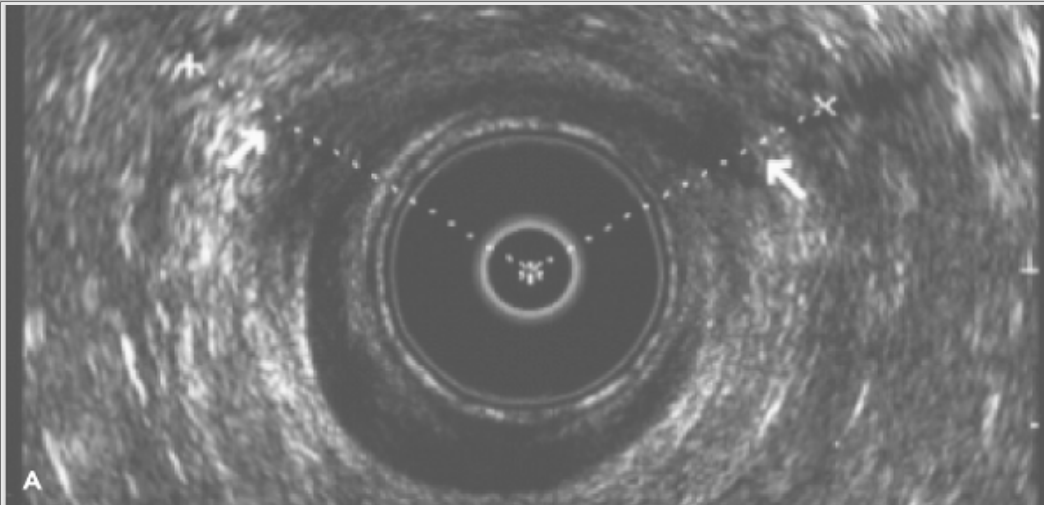
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of pelvic floor neuropathy (76). This technique measures the electrical activity arising in muscle fibers during contraction and at rest. Different types of electrodes may be employed, including surface electrodes, concentric needle electrodes, and single-fiber electrodes. Surface electrodes are less invasive because they are applied near or within the anal canal, but they are capable only of recording basic anal sphincter activity. This technique often is used in conjunction with biofeedback therapy. Concentric needle electrodes are most commonly used in anorectal physiology laboratories to selectively survey an individual muscle's activity. Insertion of the thin needlelike cannulas containing steel wire electrodes can be painful. Even smaller single-fiber EMG electrodes are used to record the activity of single muscle fibers, which can be quantified to calculate fiber density. Following denervation injury, increased muscle fiber density occurs during reinnervation. Thus, single-fiber EMG can provide indirect evidence of neurologic injury by mapping the EAS and identifying injured areas. This technique rarely is used in clinical practice. Endoanal ultrasonography offers increased patient comfort and more reliable results than EMG and has replaced this technique for the detection of EAS disruption because of increased patient comfort and more reliable results.



Figure 25.1 Bruel-Kjaer (Copenhagen, Denmark) ultrasound probe (type 1850) with a 7.0 MHz transducer (focal length, 2 to 5 cm) housed with a plastic cone.



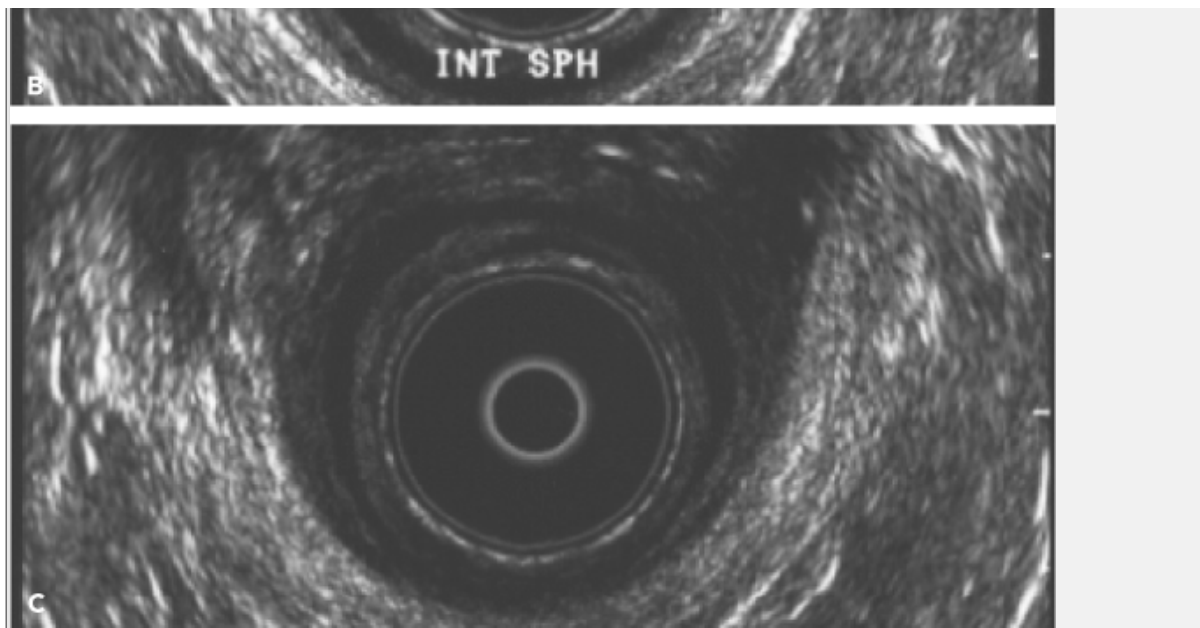


Figure 25.2 A: Endoanal ultrasound image from the distal anal canal demonstrating defects in the internal sphincter from 10 to 3 o'clock and the external sphincter from 10 to 2 o'clock. **B: Endoanal ultrasound image from the middle anal canal** demonstrating defects in the internal sphincter from 12 to 2 o'clock and the external sphincter from 10 to 1 o'clock. **C: Endoanal ultrasound image from the proximal anal canal** demonstrating an intact IAS and a normal physiologic split in the external sphincter.

Motor nerve conduction studies provide another means of measuring pelvic

floor neuropathy. The axon of a nerve is stimulated, and the time it takes the action potential to reach the muscle supplied by the nerve is recorded. The delay between stimulation and the muscle response is called the nerve latency. Pudendal nerve terminal motor latency (PNTML) can be determined by transrectal stimulation of the pudendal nerve using a St. Mark's electrode (77). A nerve stimulator is mounted on an examination glove at the fingertip (Fig. 25.3) and positioned transrectally over each ischial spine. A stimulus of up to 50 mV over a duration of 0.1 milliseconds is applied, and the latency of the EAS muscle contraction is measured. A value of 2.2 milliseconds or less is considered normal. A recent study evaluating normative values for pudendal and perineal nerve latencies observed increased latencies with increased age (78). Prolongation of the PNTML is indicative of damage to that nerve or the presence of a demyelinating condition. Pudendal nerve function has prognostic value in the surgical repair of traumatic sphincter injuries (79) and is useful in preoperative counseling.

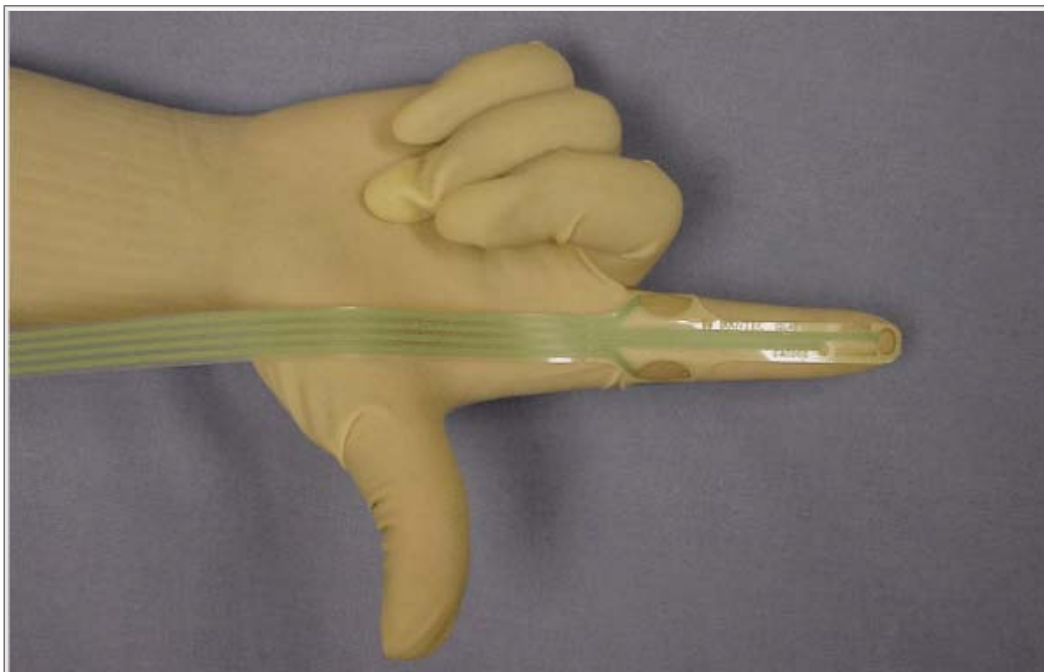


Figure 25.3 St. Mark's electrode used for measuring pudendal nerve motor terminal latency. The stimulating electrode is on the fingertip, and the receiving electrode is on the proximal finger near the knuckle.

Anal Manometry

Anal manometry is used to quantify function of the anal sphincter mechanism.

Water-perfused manometry catheters or water-filled balloons are most often used to measure anal canal pressures. Resting anal canal pressures reflect IAS function, and pressures in the lower anal canal during maximal voluntary contraction reflect EAS function. Vector analysis can be used to detect asymmetry within the anal sphincter. Anal manometry provides indirect evidence of sphincter injury; low resting tone indicates IAS injury, and decreased maximum squeeze pressures indicates EAS injury. Anal pressures are influenced by a variety of factors, including tissue compliance and muscular tone. Consequently, anal manometry results are difficult to interpret and correlate poorly with the specific anatomic defect. Interpretation is further complicated by the wide variation of normal pressure values that change with age and parity. Significant overlaps occur between manometric values for incontinent patients and those without incontinence. Thus, anal manometry may be of limited value in the evaluation and treatment of anal sphincter defects and fecal incontinence.

Proctoscopy and Flat Tire Test

Proctoscopy has an important role in the evaluation of fecal incontinence. It can be performed independently or during colonoscopy, flexible sigmoidoscopy, and flat tire test. **Proctoscopy can detect anorectal pathology, such as prolapsing hemorrhoids, intussusception, ulcerative or radiation proctitis, or a solitary rectal ulcer.** The flat tire test is added when a rectovaginal or colovaginal fistula is suspected but cannot be visualized on routine office evaluation. This test usually is performed under anesthesia but can also be done in the office setting. Saline or water is placed in the vagina with the patient Trendelenberg's position. Using a proctoscope or rigid sigmoidoscope, air is instilled into the rectum. Vaginal retractors provide visualization of the posterior vaginal epithelium and vaginal apex. Observation of bubbling into the vaginal fluid confirms the diagnosis of a rectovaginal or colovaginal fistula. The rectal site of the fistula usually is identifiable, depending on the size and location of the fistula as well as the quality of the bowel preparation.

Disordered Defecation

Sitzmark Study

Colonic transit studies are performed using ingested radiopaque markers followed by serial abdominal radiography. Patients are asked to follow a high-fiber diet over the test period and avoid the use of laxatives, suppositories, or enemas. A capsule containing 20 to 24 markers is ingested initially, and abdominal radiography is performed either daily or on the fourth day, the seventh day, and every 3 days thereafter until all the markers are gone. Segmental transit times are then calculated using a mathematical formula. Colonic transit study results are used to classify patients with constipation into delayed transit, normal transit, and outlet obstruction. After day 6, there should be fewer than five markers remaining in the colon. With slow transit, more than five markers are scattered throughout the colon. With outlet obstruction, more than five markers are in the rectosigmoid region, and transit is normal throughout the rest of the colon.

Pelvic Floor Fluoroscopy and Magnetic Resonance Imaging

Pelvic fluoroscopy permits radiological evaluation of pelvic floor and anorectal anatomy and physiology. It is particularly useful in obstructive defecation disorders, such as intussusception, rectocele, enterocele, anismus, and perineal descent. The patient is placed on a radiolucent commode, and contrast material is instilled into the rectum. The addition of vaginal, bladder, and oral contrast material is helpful diagnostically when multicompartamental prolapse is suspected. A series of lateral still images or continuous imaging using videography are made with fluoroscopy while the patient is at rest, during defecation, and with contraction of the anal sphincter. Similar films can be obtained for evacuation of the bladder. Pelvic fluoroscopy has many names, including defecography,

defecating proctography, defecating cystoproctography, and colpocystoproctography, depending on the technique used. The measurements obtained include size of the rectal ampulla, length of the anal canal, anorectal angle, puborectalis motion, and pelvic floor descent. Severity of

prolapse and pelvic floor descent is quantified in relation to the pubococcygeal line. Pelvic fluoroscopy is superior to physical examination for diagnosing enterocele (80), and this technique has the advantage of being able to distinguish enteroceles from sigmoidoceles. Rectosphincteric dyssynergia may be present when the patient experiences incomplete relaxation of the puborectalis muscle during rectal evacuation, the anorectal angle is preserved, and there is incomplete emptying. Pelvic fluoroscopy is considered the definitive test for diagnosing intussusception (81), and it is the preferred technique for quantifying perineal descent.

Dynamic MRI with luminal contrast is an imaging modality similar to pelvic fluoroscopy. Its ability to detect prolapse is similar to that of fluoroscopy, but MRI can visualize pelvic floor musculature and soft tissue, thus giving it the advantage of detecting ballooning of the levator muscles and levator ani hernias. The supine position of the testing is a drawback; however, there are isolated reports of upright dynamic MRI using open scanners that show results comparable to fluoroscopy for detection of anorectal pathology (82). Fluoroscopy and dynamic MRI can be used in situations involving severe multicompartmental prolapse or in which the severity of the symptoms is disproportionate to examination findings.

Anal Manometry

Anal manometry is used to determine maximum resting pressure, maximum squeeze pressure, rectal sensation and compliance, as well as the presence of an intact rectoanal inhibitory reflex. With disordered defecation, it can be used to diagnose Hirschprung disease and anismus. The addition of surface EMG to document relaxation helps exclude anismus as a cause of obstructed defecation. Failure of the anal sphincter to relax with defecation and increased electrical activity of the EAS and puborectalis are seen in patients with anismus. In contrast, there should be no increase in the electrical activity measured by surface electrodes for patients with Hirschprung disease.

Colonoscopy and Proctoscopy

Standard gastrointestinal evaluation for patients with symptoms of disordered defecation should include a barium enema or colonoscopy to eliminate the possibility of colorectal malignancy. Proctoscopy should be included as part of the routine examination because it may reveal anorectal pathology..

Therapeutic Approach to Fecal Incontinence

Treatment of fecal incontinence should first focus on nonsurgical options, including dietary modification, medical therapy, and biofeedback. Any underlying systemic conditions or gastrointestinal disorders should be treated before initiating an extensive evaluation for other causes of fecal incontinence. If symptoms persist, further investigation should be undertaken. If the evaluation discloses an underlying EAS defect and conservative therapy has been unsuccessful, it is reasonable to proceed with surgical treatment.

Following is an overview of treatment options and the efficacy of each approach. The lack of a consistent outcome measure makes it difficult to compare efficacy among treatments. Some studies base success on strict conformity with criteria for continence, but the results vary for continence of flatus, liquid, or solid stool. Other studies base success on more subjective criteria, such as improvement following treatment. Daily diaries can be maintained, but the results may be unreliable. Even if a validated symptom survey and quality-of-life scale are employed, few studies use the same outcome measure.

Nonsurgical Treatment

Nonsurgical management focuses on maximizing the continence mechanism through alteration of stool characteristics or behavioral modification. Stool consistency and volume can be manipulated by dietary and pharmacologic means to achieve passage of one to two well-formed stools per day. The rationale for this approach is that formed stool is easier to control than liquid stool. Additionally, behavior modification can be employed using bowel regimens that focus on the predictable elimination of feces. Physical therapy and biofeedback can also be useful for strengthening the continence mechanism.

Pharmacologic Approaches

Dietary Modification and Fiber

Dietary modification for treatment of fecal incontinence frequently involves avoidance of foods that precipitate loose stools and diarrhea. Common dietary irritants include spicy foods, coffee and other caffeinated beverages, beer and alcohol, and citrus fruits. Avoidance of dairy products or the addition of lactase dietary supplements is essential for those with lactose intolerance. The addition of fiber may improve fecal incontinence by functioning as a stool bulking agent to increase volume and density. The average individual in the United States consumes less than one half of the recommended daily fiber intake (25–35 g). Various fiber sources are listed in Table 25.7, with the highest content found in fiber cereals. It is difficult to consume the recommended daily amount from diet alone, and fiber supplements often are required. Although the increased stool volume and density helps many individuals maintain continence, excessive fiber with inadequate fluid intake may predispose elderly patients to fecal impaction.

Constipating Agents

Constipating agents have the most value in patients with chronic loose stools or diarrhea. They can also help improve symptoms in patients with fecal frequency and urgency. *Loperamide (Imodium)* and *diphenoxylate hydrochloride with atropine (Lomotil)* are the most commonly used agents. *Loperamide* has been shown to prolong transit time and stimulate anal sphincter function. With either of these agents, careful titration is recommended

to prevent the primary side effect of constipation. It is generally preferable

to begin using 2 to 4 mg of *loperamide* daily and then titrate up to 4 mg three to four times per day. A 4-mg dose before meals has been shown to increase anal tone and improve continence (83). *Lomotil* is started at a dose of 1 to 2 tablets every day or every other day and titrated up to 1 to 2 tablets three to four times a day as needed. Caution should be exercised for patients taking other anticholinergic medications. Anticholinergic side effects include dry mouth, drowsiness, lightheadedness, and tachycardia. *Codeine* can also be used as a constipating agent. It should be used judiciously in those with chronic disorders and in elderly patients because of side effects common to narcotics, including addiction with prolonged usage and central nervous system and respiratory depression. A study of 82 geriatric patients documented the efficacy of pharmacologic treatment for fecal incontinence (84). Patients were treated based on the underlying cause. Those with fecal impaction received lactulose and enemas, whereas those with neurogenic fecal incontinence received codeine phosphate as a constipating agent and enemas. The rate of cure for fecal incontinence was 60% in the treatment group versus 32% for controls ($P < 0.001$).

Table 25.7 Fiber Sources

<i>Cereals</i>		<i>Fiber Supplements</i>	
All-Bran Extra Fiber (1/2 c)	15 g	Konsyl (1tsp)	6.0 g
Fiber One (1/2 c)	14 g	Perdiem (1tsp)	4.0 g
Raisin Bran (1/2 c)	7 g	Metamucil (1tsp)	3.4 g
All Bran (1/2 c)	6 g	Maalox w/fiber (1 tbs)	3.4 g
Fruit & Fiber (2/3 c)	5 g	Mylanta w/fiber (1tsp)	3.4 g
Frosted Mini Wheats (1/2 c)	3 g	Citrucel (1tbs)	2.0 g
<i>Breads</i>		<i>Vegetables</i>	
Whole wheat (1 slice)	2.0 g	Lettuce (1 c)	1.4 g
White (1 slice)	0.5 g	Celery (1)	0.5 g
Bagel (1)	1.0 g	Tomato, raw (1)	1.0 g

Modified from **Ellerkmann MR, Kaufman H.** Defecatory dysfunction. In: **Bent AE, Ostergard DR, Cundiff GW, et al, eds.** *Ostergard's urogynecology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:362, with permission.

Medications for Irritable Bowel Syndrome

Dietary treatment of IBS consists of avoiding foods that are associated with symptoms, including alcohol, caffeine, sorbitol, and foods that increase gas production. Although increased dietary fiber or fiber supplementation has been shown to improve the constipation-predominant form of this illness, fiber supplementation has little effect on the diarrhea variant associated with fecal incontinence. Pharmacologic therapy is directed toward the predominant symptom. *Loperamide* and *Lomotil* tend to be useful first-line agents for treating diarrhea. Tricyclic antidepressants improve abdominal discomfort and are also

valuable in diarrhea–predominant patients because of their constipating effect. The serotonin type 3 (5HT3) antagonist *alosetron* (*Lotronex*) has been approved by the U.S. Food and Drug Administration for the treatment of severe diarrhea–predominant IBS refractory to treatment. It has shown improvement in global assessment measures, but its use is limited because of multiple isolated case reports of ischemic colitis. The recommended dose is 1 mg once or twice daily. It does not appear to be effective for the spastic–pain variant of IBS. Anticholinergics (*dicyclomine*, *hyoscyamine*) and antispasmodics (*mebeverine*, *pinaverine*) are targeted at the pain and bloating symptoms but may also be useful for the diarrhea variant because of their constipating side effects. Studies comparing anticholinergic medications to placebo show inconclusive results with only modest benefits. Antispasmodic agents may also be of value and are available in many countries but are not approved for use in the United States. Currently, additional 5HT3 antagonists and 5HT4 antagonists are under development. Most studies are poorly designed and difficult to interpret because of a high placebo response rate that often exceeds 30% (85,86).

Behavioral Approaches

Biofeedback

Biofeedback can be an effective therapeutic modality provided patients are motivated and comprehend instructions. The two proposed mechanisms through which biofeedback improves fecal continence are afferent and efferent training. Afferent training focuses on improving sensation in the anorectal canal through recruitment of adjacent neurons to decrease the sensory threshold of volume stimulation. The goal of this training is to enhance and restore anal sensation and the rectoanal inhibitory reflex. Efferent training enhances and restores voluntary contraction of the EAS, which permits additional recruitment of motor units and stimulates muscle hypertrophy. These two methods of training can be performed independently, but are often combined for additional therapeutic benefit. The most common training method uses an intrarectal balloon. The balloon acts to stimulate rectal distention and provide pressure feedback from coordinated or synchronized contraction of the

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pelvic floor muscles. Other techniques focus on strength training of the EAS alone using anal pressure feedback or EMG or afferent training alone using an intrarectal balloon without pelvic floor muscle contraction in response to the stimulus.

More than 35 studies have been done to evaluate the efficacy of biofeedback for treatment of fecal incontinence, and several excellent review articles and meta–analyses have determined the effects of individual treatments and predictors of patient response to treatment (87,88,89). The results of all of these studies uniformly agree that biofeedback and pelvic floor exercises improve fecal incontinence and have a role in clinical practice. They also agree that the existing literature is fraught with methodologic problems and lacks validated outcomes and controls. Thus it is difficult to compare directly the study results.

Biofeedback is an ideal first–line therapy because it offers an effective, minimally invasive treatment without any reported adverse events. Biofeedback also appears

to provide a higher probability of successful outcome than standard medical care for treating functional fecal incontinence (67% versus 36%, respectively, $P < 0.001$) (87).

A **Cochrane review of biofeedback and exercises for treatment of fecal incontinence** found only five randomized or quasirandomized control trials that qualified for inclusion (90). The authors concluded that **there is insufficient evidence to evaluate the efficacy of exercises and biofeedback for treatment of fecal incontinence**. Specifically, they were not able to determine which patients are suitable for treatment, nor which method of treatment is optimal. A meta-analysis of biofeedback techniques included a review of 13 studies using strength training alone, 4 studies with sensory training alone, and 18 with coordinated sensory and strength training (89). The authors found no advantages between coordinated training (67% improved) and strength training (70% improved). However, strength training using EMG appeared to be better than strength training with anal canal pressure biofeedback (74% versus 64% improved, respectively, $P < 0.04$). The limitations of this study and the literature were acknowledged.

A large randomized control trial of biofeedback for fecal incontinence in 171 patients, divided into four treatment groups, showed no significant benefit when comparing standard care to similar care with the addition of biofeedback (54% versus 53% improvement, respectively) (91). In all groups, there was a high median rating of change of symptoms and median satisfaction with benefits relatively maintained at 1-year follow-up. All groups also displayed improvement in the validated symptom surveys and quality-of-life measures as well as in anal sphincter function. The authors concluded that interactions with the therapist, patient education, and development of better coping strategies seem to be the most important factors for improvement rather than pelvic muscle exercises or biofeedback. Additional benefit may be derived with augmented biofeedback using electrical stimulation (92).

There are no clear indicators to predict which patients will benefit from biofeedback. Potential factors include age, duration and severity of incontinence, prior treatments or surgery, and severity of neurologic or physical damage. Controversy exists as to whether response to biofeedback is dependent on the presence of a structurally intact anal sphincter or normal pudendal nerve function (93,94,95,96). There is an obvious need for well-designed control trials using validated symptom surveys and quality-of-life instruments. More objective measures are desirable, and studies should carefully document duration of treatment and length of follow-up.

Bowel Regimens

The goal of bowel regimens is to achieve predictable elimination of feces. This can be accomplished by using the gastrocolic reflex as well as by dietary and pharmacologic means. Defecation immediately following meals involves the physiologic response of the

gastrocolic reflex to facilitate predictable emptying. The strength of the gastrocolic reflex varies among individuals and may be hypoactive or hyperactive with certain systemic

disorders, such as diabetes and multiple sclerosis. This technique can be especially useful in the morning to give the individual freedom from fecal incontinence throughout the day. The use of suppositories or enemas in the morning or at night in conjunction with the gastrocolic reflex may provide further relief of daytime symptoms. The goal is to leave the rectum empty between evacuations. Enema use, typically once or twice daily, should be titrated to the patient's baseline colonic activity. **Regular toileting in elderly patients in nursing homes can improve fecal incontinence caused by overflow incontinence from fecal impaction.** The use of cone-tip colostomy-irrigation catheters is reserved for patients in whom other therapeutic modalities have failed. These catheters avoid the risk of rectal perforation and provide a dam to prevent efflux of the irrigating solutions (97).

Surgical Treatment

In general, surgical treatment should be employed after conservative measures have failed. Although there may be exceptions to this principle, most surgeons follow this recommendation because of the poor long-term outcomes and high complication rates with surgery for fecal incontinence.

Overlapping Sphincteroplasty

Overlapping sphincteroplasty is the procedure of choice for fecal incontinence caused by a disrupted anal sphincter. Most authorities believe that an overlapping technique is superior to an end-to-end repair, although there are few direct comparisons in the literature. The rationale for the overlapping technique is that a more secure repair can be accomplished by placing sutures through the scarred connective tissue rather than the sphincter muscle. Sutures should be less likely to tear through or pull out of connective tissue than muscle. Therefore, the key component of the overlapping technique is preservation of the scarred ends of the ruptured EAS for suture placement.

Technique

The initial step involves wide mobilization of the ruptured EAS without excision of the scarred ends of the sphincter. This is accomplished through an inverted semilunar perineal incision or a transverse incision near the posterior vaginal fourchette with inferiolateral extension. The latter incision facilitates repair in patients with damage to the rectovaginal septum attachment to the perineal body. Patients with EAS defects have either a band of intervening fibrous scar tissue between the viable muscular ends of sphincter or a complete separation with scar tissue present only on the ruptured ends of the sphincter. In the presence of complete separation of scar tissue, perineal body reconstruction usually is indicated at the time of repair to restore normal anatomy. A Peña muscle stimulator aids in identification of the distal ends of the EAS and differentiates viable muscle tissue from scar tissue. The stimulator can be used to outline the sphincter before incision as well as during the dissection. It is important to apprise the anesthesiologist of the stimulator usage so that paralytic agents are avoided.

Excessive lateral dissection of the EAS past the 3 and 9 o'clock positions should be avoided as this is where the inferior rectal branches of the pudendal nerve innervate the EAS. Moderate bleeding often is encountered during this dissection, and the use of needlepoint electrocautery can maximize hemostasis. Controversy exists regarding the need to separate the EAS and IAS before repair. Identification of the intersphincteric groove facilitates dissection of the EAS. Dissection in this plane is relatively simple and avoids damage to either sphincter. Defects in the IAS can be more difficult to visualize because this muscle is intimately associated with the rectal mucosa. Examination with a finger in the anal canal is often helpful.

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The reconstruction begins with repair of an existing IAS defect using a 3–0 delayed absorbable monofilament suture. Next, the EAS defect is repaired with the primary goal of overlapping at least 2 to 3 cm to ensure adequate bulk of sphincter muscle encircling the anal canal. The EAS is overlapped using three to four mattress sutures of 2–0 delayed absorbable monofilament suture through the distal scar tissue. Once the sutures are tied, there should be resistance palpable with placement of a finger in the anal canal. Copious irrigation is performed throughout the procedure. Following sphincter repair, a perineal body reconstruction and rectocele repair should be undertaken, if indicated, to maximize the normal continence mechanism. Finally, the perineal skin is closed with interrupted absorbable monofilament sutures. Closure frequently requires modification of the initial incision because of changes in the perineal architecture that result from the repair. The most common approach is an inverted Y-shaped closure of the incision (Fig. 25.4).

Some surgeons recommend the overlapping repair regardless of whether it is performed immediately postpartum, delayed postpartum, or several years after obstetric injury. Performance of the overlapping technique is difficult immediately postpartum and requires

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adequate anesthesia, exposure, and equipment. Many surgeons believe that this can only be accomplished in the operating room. This repair lacks the theoretical advantage of using scar tissue to improve suture holding; however, it maximizes surface area for scarification of the sphincter ends. For a delayed postpartum repair, it is recommended to wait 3 to 6 months to permit complete resolution of inflammation and reinnervation. Two randomized control trials compared end-to-end approximation to overlapping sphincteroplasty

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(98,99). One study randomized 112 primiparous women undergoing immediate repair of a third- or fourth-degree sphincter tear (99). The authors did not detect any significant differences in objective or subjective outcomes between either of the two repairs at 3 months follow-up. Approximately one half of the women had minor alteration in fecal continence, whereas 7 (6%) had daily soiling. Despite good symptomatic results, 74 (66%) had full-thickness EAS defects on endoanal ultrasonography. The other randomized trial involved a delayed repair in

23 patients more than 1 year following delivery (99). The scar was preserved for each repair, and a puborectalis plication was performed. At a median follow-up of 18 months, there were no detectable differences in continence scores; however, the study was clearly underpowered.

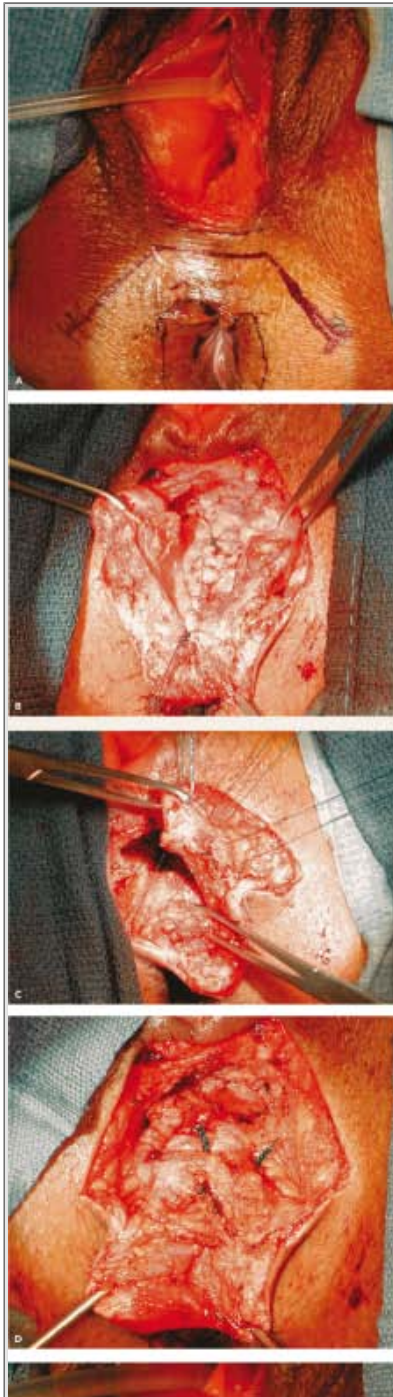




Figure 25.4 Overlapping sphincteroplasty procedure. A: Inverted semilunar perineal incision with the distal ends of the external sphincter outlined using the Peña muscle stimulator. B: The external sphincter has been dissected, the scar divided in the midline, and the internal sphincter repaired. C: The external sphincter is overlapped using three mattress sutures of 2-0 delayed absorbable monofilament suture through the distal scar tissue. D: The sutures are tied. E: The skin is closed.

Efficacy

Despite the many large series reporting the outcomes of overlapping sphincteroplasty, almost all are retrospective in nature and lack validated measures of symptom severity and quality-of-life considerations. Several overlapping sphincteroplasty series with a total of 891 patients were evaluated from 1984 to 2001. Although the length of follow-up was variable, the results showed excellent and good outcomes in approximately two thirds of patients (median 67%, range 52%–83%) (100). None of these studies had long-term outcomes.

More recent studies suggest poor long-term outcomes for the overlapping sphincteroplasty. In a series of 55 women who underwent overlapping sphincteroplasty for fecal incontinence secondary to obstetric trauma (101), researchers contacted 47 (86%) patients by postal questionnaire and telephone interview with a median time since surgery of 77 months (range 60–96 months). The investigators observed less symptomatic improvement when compared with the results at 15 months postoperative evaluation. After excluding one patient because of Crohn disease, eight (17%) failed because they required additional surgery, such as colostomy, postanal repair, and artificial bowel sphincter. Among the remaining 38 patients, 27 (71%) reported improved bowel control, 5 (13%) were unimproved, and 6 (16%) were worse. No patient was fully continent to solid and liquid stool and flatus. Only 23 (50%) patients had “good” outcomes defined as not requiring further continence surgery and fecal incontinence less than once per month.

In another study, investigators contacted 49 (69%) of 71 patients by telephone interview (102). All underwent overlapping sphincteroplasty with a median follow-up of 62.5 months (range 47–141 months). Only 6 (12%) patients were totally continent, and another 18 (37%) were continent to liquid and solid stool. In other words, more than half of the patients had incontinence to liquid or solid stool. The largest series with long-term follow-up involved contact of 130 (71%) of

191 patients using a postal or telephone questionnaire (103). The median time from surgery for respondents was 10 years (range 7–16 years). Of those who responded, 6% had no incontinence, 16% were incontinent of flatus only, 19% had soiling only, and 57% were incontinent of solid stool. These outcomes were significantly worse than the previously reported 3-year assessment (104). Despite the fact that 61% had a poor outcome defined as having fecal incontinence or requiring additional surgery for incontinence, 62% still considered their bowel control to be better than before surgery, and 74% were satisfied with the results of their surgery. Thus, although control may be improved when compared with preoperative status, continence outcomes do not seem to be maintained at long-term follow-up.

The cause of this deterioration in long-term outcomes is unknown. Possible explanations include weakening of the muscles with normal aging, repair breakdown, and underlying nerve damage from either obstetric injury or the repair itself. A problem with most studies is the lack of a follow-up ultrasonography to determine if the repair is intact. The effect of

pubdental nerve function on overlapping sphincteroplasty is somewhat controversial. Significantly lower success rates have been shown in a comparison of those with normal pudendal nerve terminal motor latencies to those with abnormal latencies (63% versus 17%, $P < 0.01$) (105). Other studies have confirmed this finding (79,106,107), but the more recent studies fail to show a difference based on preoperative neurophysiologic testing (101,103). Other controversial factors that may affect outcome include age, duration of fecal incontinence, size of the defect, and anal manometry results.

Although there are many controversial aspects to overlapping sphincteroplasty, the literature is in agreement that **diverting colostomy is not necessary** (99,108,109); bowel confinement does not improve outcomes (99,108,110); clinical improvement correlates with postoperative endoanal ultrasonography results (101,111,112); and prior sphincteroplasty does not affect outcomes (105,111,113).

Subsequent Deliveries

Multiple studies confirm the impact of anal sphincter laceration during the first delivery on the risk of a sphincter laceration in a second delivery (114,115,116). These studies have calculated odds ratios ranging between 2.5 and 5.3 for a second sphincter disruption. Two recent population-based studies revealed adjusted odds ratios of 4.2 (95% CI, 3.9–4.6) and 4.3 (95% CI, 3.8–4.8) (115,116). These odds ratios probably represent underestimates because they do not take into account higher cesarean delivery rates in subsequent births for women with a history of sphincter laceration. Both of these studies observed significantly increased risk of recurrent sphincter laceration associated with increased birth weight. The studies estimated that approximately 25 cesarean deliveries have to be performed to prevent one recurrent sphincter laceration. In fact, only 10% of women with anal sphincter lacerations at second delivery had a history of prior sphincter laceration. Therefore, **although a history of prior sphincter laceration increases the risk of recurrent sphincter laceration, the risk remains relatively small**. Nevertheless, it is important to accurately counsel expectant mothers about their risk of sphincter laceration. Using

this information, they can decide whether the risk of recurrent laceration outweighs the risk of elective cesarean birth. The risk of subsequent vaginal delivery on symptoms of fecal incontinence is unknown for women with a repaired anal sphincter. The presence or absence of pre-existing fecal incontinence, as well as the estimated fetal weight, should be considered in counseling for a subsequent pregnancy.

Graciloplasty

Surgical reconstruction with a muscle flap should be considered in cases in which there is insufficient muscle to repair the EAS and all conservative measures have failed. Insufficient muscle can be caused by trauma or severe atrophy that results from denervation injury and congenital disease. Most patients considering this procedure have already undergone an overlapping sphincteroplasty that failed. Graciloplasty, first described by Pickrell et al. in 1952 (117), is a skeletal muscle transposition procedure that uses the gracilis to create a new anal sphincter. There are three suitable muscles for this type of procedure: the gracilis, sartorius, and gluteus maximus. Ideally, the muscle should be easily mobilized and transposed but not essential for locomotion or posture. The sartorius and gluteus maximus are suboptimal because the sartorius receives segmental vascularization, which restricts rotation, and the gluteus maximus is important in daily activities such as running, climbing stairs, and rising from a sitting position. **The gracilis is a better choice because it can easily be mobilized without damage.** As the most superficial adductor, it receives neurovascular supply proximally and has no important independent function.

Technique

Either one long incision or three small incisions are made in the medial thigh. The gracilis muscle is identified and mobilized toward its insertion onto the medial aspect of the tibia where the tendon is divided. Anterior and posterior perianal incisions are made approximately 1.5 cm from the anal verge. Tunnels are developed in the extrasphincteric space and from the proximal thigh to the anterior perianal incision. The gracilis muscle is then gently delivered to the anterior perianal incision, guided around the anus to the posterior perianal incision, and returned to the anterior incision encircling the anal canal. The distal tendon of the gracilis is passed behind the muscle and anchored to the contralateral periosteum of the ischium. In cases when there is inadequate length, it can be sutured to the ipsilateral ischium. This procedure can also be performed bilaterally. In patients with a large rectovaginal fistula or cloaca, a myocutaneous flap can be mobilized and used to help close the defect. Improvement of fecal incontinence is caused by passive increase of the resistance of the anal canal by the bulk of the encircling muscle (Fig. 25.5).

Experimental efforts to improve the efficacy of this procedure have focused on developing resting tone in the transposed muscle through the use of an implanted neurostimulator. The intent of the stimulated graciloplasty is to convert the fast-twitch muscle fibers into slow-twitch muscle fibers, which are more fatigue resistant. Initially, implantation of the pacemaker was performed at 6 weeks after the graciloplasty, but now most are performed

concomitantly. Stimulation can be applied directly to the obturator nerve or intramuscularly to the nerve branches inside the muscle. The muscle is stimulated at a cyclic frequency, with gradual increases every 2 weeks. After 2 months, continuous stimulation is performed. Stimulation is adjusted to maintain tonic contraction around the anus, and it is interrupted or turned off to defecate.

Efficacy

An exhaustive review of the published literature identified 37 articles of patients undergoing dynamic graciloplasty (118). Most of these articles were case series, and there were no randomized trials or cohort studies evaluating safety and efficacy. Mortality rate was 1% (range 0%–13%, 95% CI, 1%–3%) after excluding cancer deaths. There was a high rate of morbidity (1.12 events per patient). Thus, most patients will have at least one adverse event, and several will have multiple complications. There is also a very high reoperation rate. The most common complications were infections (28%), stimulator and lead faults (15%), and leg pain (13%). Satisfactory continence was achieved 42% to 85% of the time, although satisfaction was not defined consistently across studies. The authors concluded that dynamic graciloplasty appeared to have equal or better efficacy than colostomy but carried a higher morbidity rate. Another review of the three largest case series (119,120,121) found success rates ranging from 55% to 78%. Major infections were found in 13% to 29%, pain in 27% to 28%, and device or lead problems in 12% to 18%. More recent series containing large numbers of patients found similar results for efficacy, morbidity, and reoperation rate (122,123). High rates of disturbed evacuation also were reported.

Artificial Sphincter

The artificial anal sphincter is an alternative to a graciloplasty. This is a modification of the device originally designed to treat urinary incontinence. The current device is the Acticon® Neosphincter (American Medical Systems, Minnetonka, Minnesota, USA) (Fig. 25.6). The indications for its use are similar to those for the graciloplasty.

Technique

Implantation of the artificial anal sphincter is performed, similar to the graciloplasty, through perianal tunnels. A Silastic inflatable cuff is placed around the native sphincter

to occlude the anal canal. A pressure-regulating balloon containing radio-opaque solution is situated in the retropubic space, and a control pump is positioned in the labia majora. Activation of the control pump deflates the cuff, permitting defecation (see Fig. 25.6).

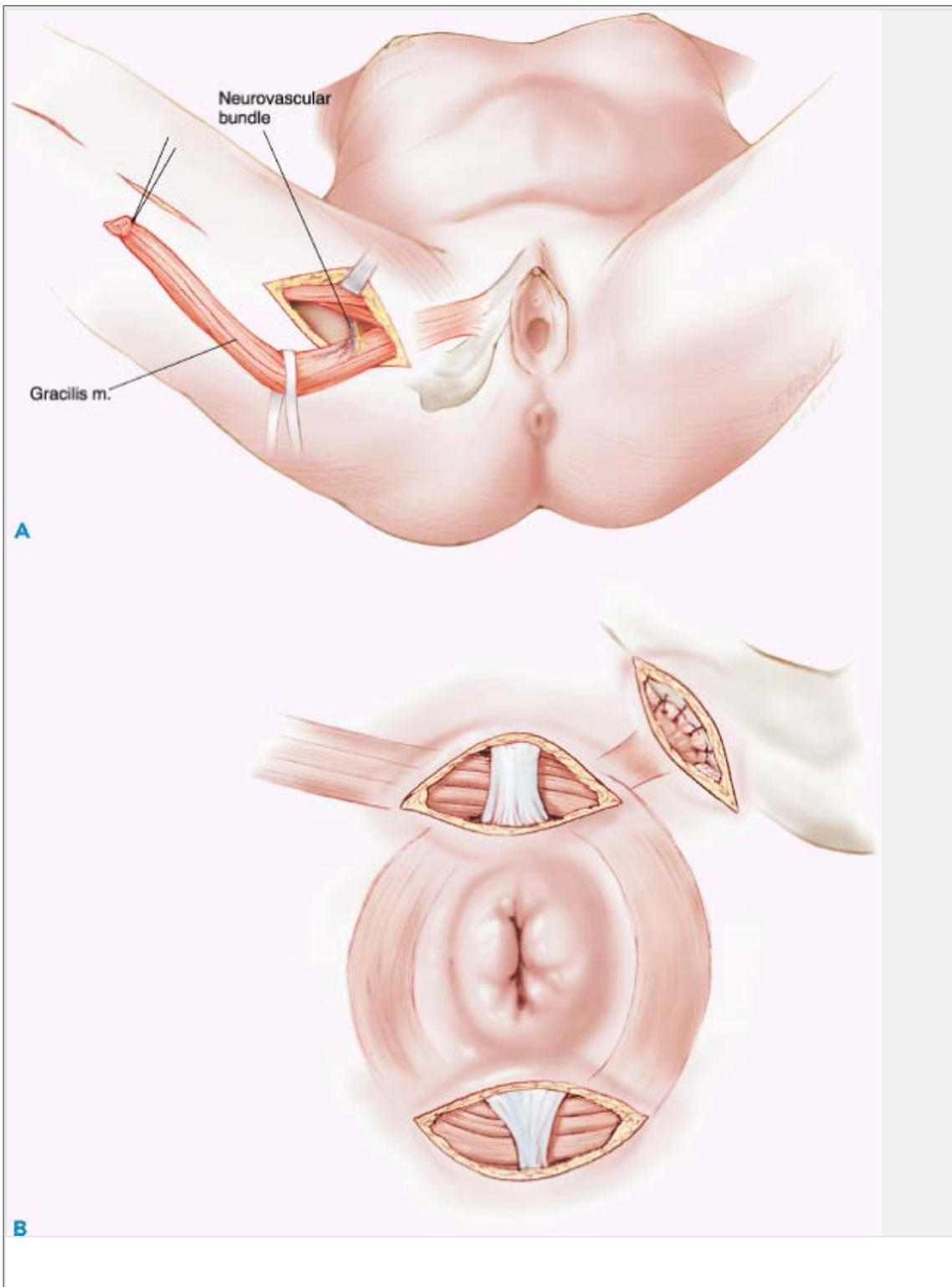


Figure 25.5 Graciloplasty. A: The gracilis muscle is identified and mobilized toward its insertion onto the medial aspect of the tibia where the tendon is divided. B: Anterior and posterior perianal incision are made approximately 1.5 cm from the anal verge. The muscle is then tunneled around the extrasphincteric space circumferentially. The distal tendon is passed behind the muscle and anchored to the contralateral periosteum of the ischium.

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Efficacy

A recent extensive review of the literature summarized 13 case series and one case report from 1996 to 2003. There were no randomized trials or cohort studies (124). The largest series consisted of 112 patients (125). There was one series with 53 patients, and all others had fewer than 28 patients apiece (126). Explantation was required in 17% to 41% of patients. Reasons for explantation included infection, erosion, device malfunction, pain, incontinence, and dissatisfaction, with infection being the most common. Surgical revision was necessary in 13% to 50% of the reports. Almost everyone had at least one adverse event, and more than one third of these events required surgical intervention. Reasons for surgical revision were similar to those for explantation. Rates of fecal impaction ranged from 6% to 83%. All studies recorded statistically and clinically significant improvement in continence scores for patients with a functional artificial sphincter; however, most did not report the continence status for those in whom the device was explanted. The proportion of patients with a functional device ranged from 49% to 85%. The authors concluded that there is insufficient evidence on the safety and effectiveness of the artificial sphincter for fecal incontinence.

One randomized control trial of 14 patients compared artificial sphincter with a program of supportive care (127). Supportive care included all aspects of conservative management,

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such as physiotherapy, dietary advice, pharmacotherapy, and advice regarding skin care, odor management, anxiety reduction, and use of incontinence aids or appliances. Significant improvements in continence scores and quality-of-life measures were seen in the artificial sphincter group but not in the control group at 6 months follow-up. Explantation rate was 14% (1 of 7 patients). Two other patients had complications, including severe fecal impaction and perineal wound erosion requiring reoperation. The authors conclude that **the artificial sphincter is safe and effective compared with supportive care alone.** They anticipate perioperative and late complications, which may require explantation in up to one third of patients. It is also remarkable that only one patient (14%) whose condition was managed conservatively had significant improvement based on continence scores, whereas the status of all others was relatively unchanged.

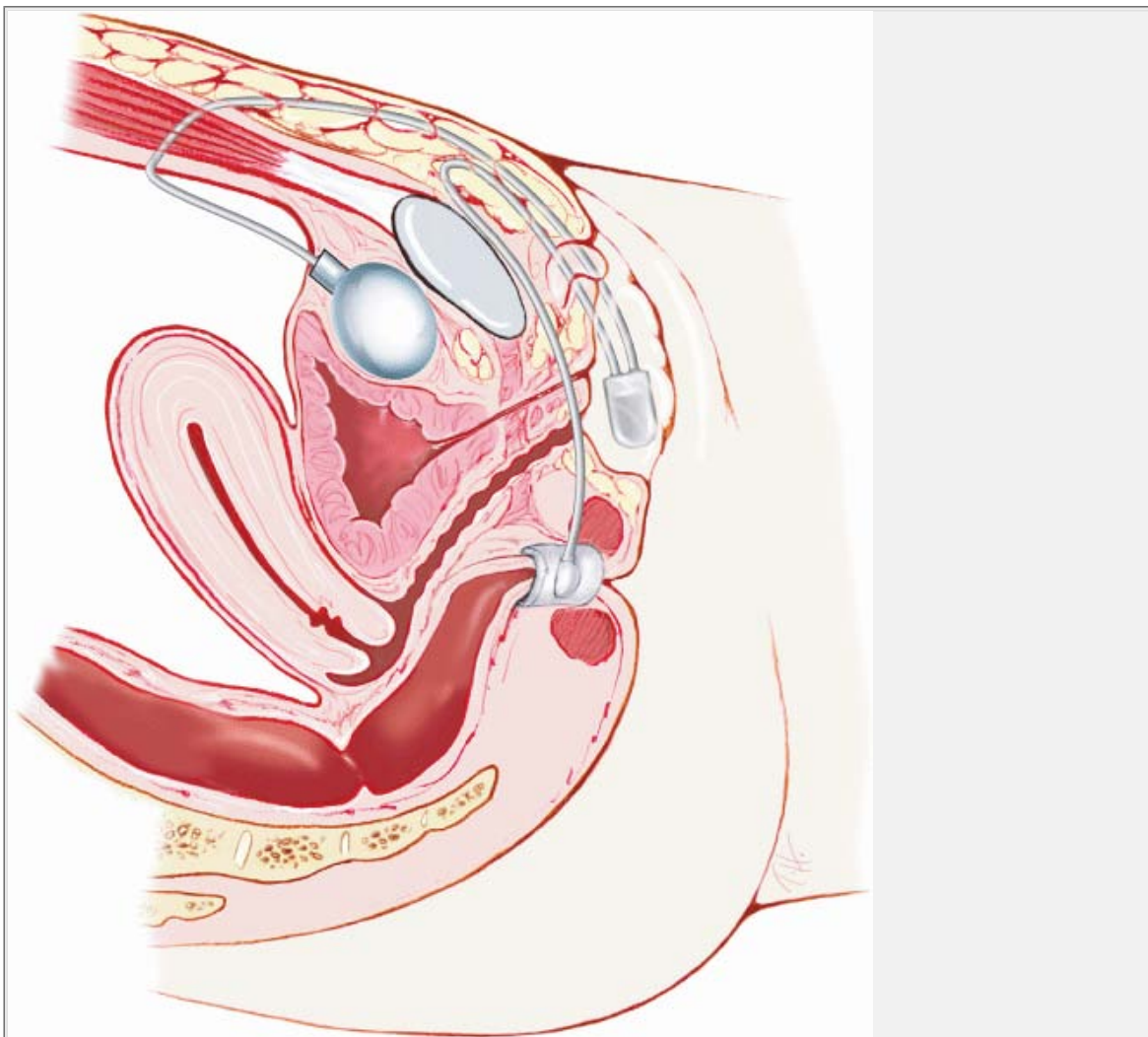


Figure 25.6 Acticon® Neosphincter. This device includes an inflatable cuff placed around the anal canal, a balloon reservoir stored behind the pubic bone, and a pump located in the labia. (Courtesy of American Medical Systems, Inc. Minnetonka, Minnesota, <http://www.AmericanMedicalSystems.com>.)

Another study compared the effectiveness of artificial sphincter with dynamic graciloplasty (128). Two surgeons each performed four consecutive operations with each technique to minimize the learning curve of a new operation. Each started with a different procedure to avoid discrepancies in the time of follow-up. This prospective cohort study involved eight patients in each group who had similar demographic variables. Length of follow-up was 44 months in the artificial sphincter group and 39 months in the dynamic graciloplasty group. Early postoperative complications were similar in each group at 50%, as were late complications, with both groups reporting a high reoperation rate of 63%. There were six (75%) late

complications in the artificial sphincter group, of which three (38%) were nonreversible and required explantation. Postoperative continence scores were significantly lower with the artificial sphincter than with graciloplasty. The authors conclude that **artificial sphincter has better efficacy and similar morbidity compared with dynamic graciloplasty**. The rate of late complications for the artificial sphincter exceeded that reported in the literature, which may indicate poor long-term durability. Postoperative continence scores reflect those reported for artificial sphincter but are far worse than those for dynamic graciloplasty. The authors feel that the learning curve with the artificial sphincter is less important than that with graciloplasty.

Sacral Nerve Root Stimulator

Sacral neuromodulation (InterStim®, Medtronic, Minneapolis, Minnesota, USA) **was approved by the U.S. Food and Drug Administration for treatment of urinary urge incontinence in 1997 and for nonobstructive urinary retention and urgency in 1999. It has been employed experimentally for the treatment of fecal incontinence.**

The exact mechanism of action has not been fully elucidated. The goal of sacral nerve stimulation is to recruit residual function of the continence mechanism through electrical stimulation of its peripheral nerve supply. Initially, indications were confined to patients with deficient EAS and levator ani function without gross morphologic defects and intact neuromuscular connections. More recently, the acceptable indications have expanded to include deficiency of the IAS, limited structural defects, and functional deficits of the internal and external anal sphincter.

Technique

The device is instilled exactly the same way as for treatment of urinary incontinence. Current application is performed as a two-stage outpatient surgical procedure. The first stage involves instillation of the electrodes. The electrode is placed through the S2–4 foramen using minimally invasive surgical technique. During the test phase, multiple electrodes can be employed either bilaterally or at different levels to determine the site with the best response. Proper location is confirmed intraoperatively using fluoroscopy as well as visualization of an appropriate pelvic floor muscle response (bellows) with minimal plantar flexion of the first and second toes, which usually corresponds to S3 stimulation. An interval testing phase utilizes an external pulse generator that typically lasts 1 to 2 weeks. Those with a good response (decrease in fecal incontinence episodes

of at least 50% documented by bowel-habit diary) will proceed to the second stage, implantation of the permanent pulse generator (IPG). Typically only one electrode is left in place at the end of the second stage. Once the permanent pulse generator is implanted, all adjustments are made using telemetry. The patient has a basic remote control that enables her to turn the device on or off and adjust the amplitude of the stimulation.

Efficacy

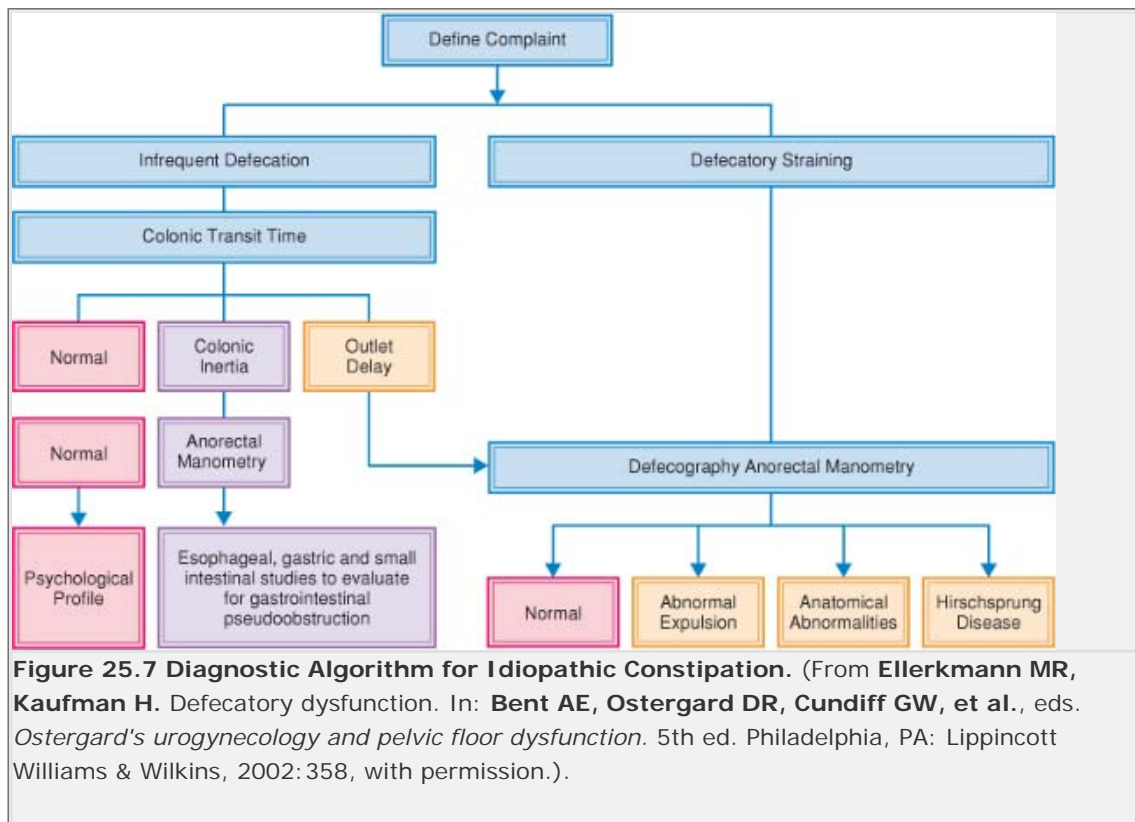
By the end of 2003, sacral nerve stimulation had been used to treat more than 1,300 patients

with fecal incontinence (129). Despite this large number, the analysis of the results is limited to several small case series. In all studies, significant improvements in continence scores lasting up to 99 months occurred. Most patients experienced at least a 75% improvement in continence scores, and improvement also occurred in the frequency of incontinence episodes, the ability to postpone defecation, and bowel emptying. Intent-to-treat analysis revealed 80% to 100% therapeutic success. There also were significant improvements in quality-of-life measures using validated measurement scales. Complications occurred in 0% to 50% of patients, with the most common complications consisting of pain at the electrode or IPG site, electrode migration, infection, or worsening of bowel symptoms. No permanent sequelae occurred, however. Effects of anorectal physiology varied among the published studies, highlighting the fact that the precise mechanism of action remains unclear.

A review of both fecal incontinence and constipation found that 149 (56%) of the 266 patients went on to permanent implantation (130). The rate of permanent implantation was higher for most studies, approximating 80%. Among implanted patients, 41% to 75% were completely continent to solid and liquid stool, and 75% to 100% had at least a 50% improvement in the number of incontinent episodes. One double-blind crossover trial with two patients had the stimulators set below the sensory threshold and turned on or off for 2-week intervals (131). The number of fecal incontinence episodes per week improved from two to zero for one patient and from ten to one for the other patient. In another review, 19 (13%) adverse events occurred in 149 patients, findings that were similar to those mentioned previously (130). **Thus, sacral nerve stimulation appears to be a promising new treatment for fecal incontinence with relatively limited complications.**

Therapeutic Approach to Constipation

As with fecal incontinence, it is imperative to attempt conservative management of constipation and defecatory dysfunction before performing surgery. Initial evaluation should focus on identifying any underlying systemic conditions (see Table 25.1) associated with disordered defecation and optimizing treatment for these conditions. In the absence of systemic etiologies, it is reasonable to proceed with empiric, nonsurgical management, such as diet, fiber supplementation, and toileting behavior. Biofeedback and laxatives can be used in more severe cases. Initially, disimpaction with regular enemas or laxatives is essential if the patient has fecal impaction. **Symptoms that persist despite a trial of conservative management indicate the need for further evaluation of colonic and anorectal function.** A diagnostic algorithm for idiopathic (nonsystemic) constipation is given in Figure 25.7. Treatment should then be tailored to the underlying cause. Some conditions associated with disordered defecation are best treated using nonsurgical techniques, whereas others may benefit from surgery once conservative management has failed. As with fecal incontinence, the lack of consistent outcome measures in the published literature makes it difficult to compare efficacy among treatments.



Nonsurgical Treatment

Nonsurgical management focuses on maximizing anorectal function through alteration of stool characteristics or behavioral modification. Stool consistency and volume can be manipulated by dietary and pharmacologic means to achieve passage of one stool every day or every other day. Additionally, behavior modification can be employed using regular toileting to prevent fecal impaction. Physical therapy and biofeedback can also be useful for coordinating pelvic floor and anal sphincter relaxation with defecation.

Pharmacologic Approaches

Dietary Modification and Fiber

The role of increased fluid and fiber intake for the treatment of constipation is controversial. For years, it has been a commonly accepted belief that constipation is caused by low fluid intake and can be improved by increasing consumption. Several studies showed no association between fluid intake and constipation (132,133,134). However, one large study

of 21,012 nursing home residents found a weak association between decreased fluid intake and constipation with an odds ratio of 1.49 (135). In one interventional study, increased fluid intake failed to improve stool frequency, consistency, or defecatory dysfunction in children (136). Another interventional study using fiber and mineral water displayed an increase in stool frequency and a decrease in laxative use in adults with constipation (137). This study lacked baseline data collection resulting in recall bias, and the use of mineral water containing magnesium may confound the results because of its mild laxative effect. Overall, the existing data do not support increased fluid intake to treat constipation unless there is evidence of dehydration (132).

The addition of fiber may improve constipation through several mechanisms. Fiber acts as a stool bulking agent and improves stool consistency through water absorption. It can also act as a substrate for bacterial proliferation and gas production. These mechanisms of action are believed to result in increased colonic motility, decreased transit time, and increased stool frequency.

Fiber therapy appears to have a beneficial effect in the treatment of diverticular disease (138), constipation of pregnancy (139), and possibly IBS (140). Its efficacy for idiopathic (nonsystemic) constipation remains uncertain. Dietary fiber intake for patients with constipation was similar to that of controls in several studies (133,134). A meta-analysis of 36 randomized trials using laxatives or fiber therapy for the treatment of constipation showed that the use of fiber or laxatives resulted in increased stool frequency and improved symptoms without the presence of severe side effects (141). Conversely, another meta-analysis showed an inability to restore transit time and stool weight in constipated patients using dietary fiber (140). Approximately one half of the patients in another study responded to fiber treatment, but a much better response occurred in patients without an identifiable structural or motility disorder (142). Consequently, a low-fiber diet may be a contributing factor in chronic constipation, and an empiric trial of fiber therapy can be expected to help some patients. Side effects of increased gas production may limit compliance with treatment, so doses should be slowly titrated. Fiber therapy should be avoided in patients with impaction, megacolon or megarectum, or obstructive gastrointestinal lesions. Fiber therapy should also be used with caution in patients with cognitive dysfunction (dementia), difficulty with ambulation, and underlying neurogenic disease for fear of worsening the condition. There is no evidence to substantiate the recommendation for extra water intake with fiber supplements (143).

Laxatives

Laxatives are commonly used to treat constipation and disordered defecation. Many classes of laxatives are available over the counter.

Bulk-forming Laxatives

These come in natural forms (*psyllium*) as well as synthetic form, (*Metamucil, Konsyl, Citrucel*), and are felt to be the safest laxatives. They have mechanisms of action and side effects similar to that of fiber (144).

Hyperosmolar Laxatives

These consist of poorly absorbed substances that increase intraluminal osmolarity and water absorption. This action results in greater stool volume with decreased consistency. Examples include nonabsorbable sugars (*lactulose and sorbitol*), *glycerin*, and *polyethylene glycol (GoLytely)*. *Polyethylene glycol* is a common preoperative bowel preparation. Side effects are diarrhea, increased flatus, and abdominal cramping (144).

Emollient Laxatives

These agents are divided into two subsets: *docusate salts* and mineral oil. The *docusate salts* have hydrophilic and hydrophobic properties similar to detergents. They soften stool and decrease surface tension by increasing stool water and lipid content. Examples include *docusate calcium (Surfak)*, *docusate potassium (Dialose, Kasof)*, and *docusate sodium (Colace, Comfolax)*. They also improve the absorption of other laxatives and are combined in preparations with stimulant laxatives such as *Correctol*, *Peri-Colace*, and *Feen-a-Mint*. The limited absorption of mineral oil allows it to penetrate and soften the stool. It can be used orally or rectally. Prolonged daily use can lead to decreased absorption of the fat-soluble vitamins A, D, E, and K. Use of mineral oil should be avoided in elderly and debilitated patients, as well as in those with esophageal motility disorders because of the potential for aspiration pneumonia. Side effects include diarrhea, anal leakage, and pruritis ani (144,145,146).

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Saline Laxatives

These usually contain magnesium cations and phosphate anions that are relatively nonabsorbable and produce an osmotic gradient with increased water absorption. They also stimulate intestinal motility by increasing cholecystokinin release. Fast-acting effects can be seen with both oral (2–6 hours) and rectal (15 minutes) preparations. Examples include *magnesium citrate*, *magnesium hydroxide (Milk of Magnesia)*, *magnesium sulfate*, *sodium phosphate*, and *biphosphate (Phospho-soda, Fleet enema)*. Although generally well tolerated, electrolyte abnormalities can occur. These side effects should be avoided in patients with renal insufficiency because of the potential for magnesium toxicity (144,145,146).

Stimulant Laxatives

These are found in three basic types: *castor oil*, anthraquinones, and *diphenylmethanes*. A metabolite of *castor oil*, *ricinoleic acid*, increases intestinal motility and secretion. Anthraquinones (*casacara sagrada*, *senna [Senekot]*, *casanthranol [aloe]*, and *danthron*) are absorbed by the small intestine and stimulate motility by increasing intraluminal fluid and electrolyte content. *Diphenylmethanes (phenolphthaleins [Feen-a-Mint, Correctol] and bisacodyl [Dulcolax])* have a mechanism of action similar to anthraquinones. These agents are potent and are intended for short-term use in cases refractory to bulk or osmotic laxatives.

It has been a long-standing belief that prolonged use can lead to a dilated atonic colon known as cathartic colon syndrome, melanosis coli, or neuronal degeneration. A recent article refutes the theory that stimulant laxatives damage the autonomic nervous system when used at recommended doses (132). Other side effects include cramping, nausea, and abdominal pain (144,145,146).

Prokinetic Agents

Medications that stimulate gastrointestinal motility primarily through neuromodulation of acetylcholine levels include *metoclopramide*, *cisapride*, cholinergic agonists (*bethanechol*), *cholinesterase inhibitors (neostigmine)*, and serotonin agonists. Their efficacy in the treatment of chronic idiopathic constipation is uncertain. *Metoclopramide* is better for upper gastrointestinal motility disorders, whereas *cisapride* appears to exert its effect at the level of the colon (144,145,146).

Behavioral Approaches

Behavioral techniques such as biofeedback and bowel regimens may have a role in certain conditions associated with constipation and defecatory dysfunction. Overall, these approaches have far less application to disordered defecation than to fecal incontinence. Biofeedback is important in the treatment of anismus. Relaxation techniques and behavioral modification may be helpful for IBS. Bowel regimens in conjunction with **laxatives, suppositories, and enemas can** facilitate emptying by optimizing the gastrocolic reflex and increased peristaltic activity.

Efficacy of Nonsurgical Treatment

Irritable Bowel Syndrome

The most commonly used first-line treatment for the constipation variant of IBS is fiber supplementation and osmotic laxatives. The efficacy of bulking agents for this condition is controversial, and many studies, including meta-analyses, exhibit an effect similar to placebo. There may be benefit to the use of fiber because of the high placebo effect with IBS treatment and lack of serious adverse events associated with its use. However, patients may experience exacerbation of bloating and abdominal discomfort with fiber therapy. There are limited data (no randomized control trials) to determine the efficacy of osmotic laxatives. They can be useful as adjunctive treatment options, but can also exacerbate abdominal pain and discomfort. A newer class of drugs, serotonin 5HT₄ agonist

tegaserod (Zelnorm), stimulates peristalsis, increases colonic motility, decreases intestinal transit times, and reduces visceral hypersensitivity. The recommended dose is 6 mg twice daily. Randomized trials have consistently shown an approximately 10% greater improvement in global IBS symptoms when compared with placebo. Improvement in the bloating and pain symptoms also occurred. No episodes of ischemic colitis or cardiac toxicity have been

reported with the use of this medication, and the most common side effects are diarrhea and headache. *Cisapride*, a 5HT₄ agonist with partial 5HT₃ antagonist actions, has been withdrawn from use secondary to rare cardiac toxicity. Additional 5HT₄ agonists, 5HT₃ agonists, and cholecystokinin antagonists are in development (85,86).

Colonic Inertia and Slow-Transit Constipation

Patients with slow-transit constipation tend to respond poorly to fiber supplementation, although most have already tried an empiric trial of fiber before testing to confirm the diagnosis (142). Some patients may benefit from regular toileting, either in the morning or after meals when there is increased colonic motor activity. Biofeedback may have modest short-term benefits, but the long-term effect is questionable (147). Enemas and suppositories can be used in conjunction with bowel regimens. It is also reasonable to attempt a trial of any of the laxatives listed in Table 25.8. Stimulant laxatives commonly are used, but questions remain about the development of neuronal degeneration with prolonged usage. It is imperative that patients adhere to and not exceed the recommended dosages. Data regarding laxative use for this condition have failed to show a significantly better response than placebo. Prokinetic agents are intuitively the ideal choice to stimulate colonic motility. Currently there is only one available prokinetic agent, *tegaserod*, approved for the treatment of constipation that improves colonic transit. Its data are almost entirely based on treatment of IBS, and there is a lack of information for its use in slow-transit constipation. Other prokinetic agents in various stages of testing include *bethanechol*, *neostigmine*, *cholecystokinin antagonists*, *misoprostol*, *colchicine*, *neurotrophin-3*, and other 5HT₄ agonists such as *prucalopride* and *mosapride* (40).

Anismus

As with slow-transit constipation, initial management using bowel regimens, laxatives, enemas, suppositories, and fiber supplementation is appropriate for patients with anismus, yet many will have already tried conservative management before undergoing testing to confirm the diagnosis. These treatments are relatively well tolerated with few serious side effects. They have not been shown to have greater efficacy when compared with placebo, and their role in the treatment of anismus remains uncertain.

Specific treatment for this condition tends to focus on biofeedback because of studies indicating that this is an acquired behavioral disorder of defecation. Modalities such as diaphragmatic muscle training, simulated defecation, and manometric or electromyography-guided anal sphincter and pelvic muscle relaxation have been employed independently or combined with other techniques. These techniques have yielded symptomatic improvement in approximately 60% to 80% of patients. Many patients with dyssynergic defecation also have abnormal rectal sensation, so rectal sensory conditioning may provide additional benefit (28,40,148,149). Others have tried *botulinum toxin* injections to paralyze the puborectalis and anal sphincter muscle. Small case series have shown modest early improvement but the results do not appear to be long lasting (150,151).

Pessary for Treatment of Pelvic Organ Prolapse

Pessaries of various shapes and sizes have been used for centuries to treat pelvic organ prolapse (152). They are a safe alternative to surgery, with the most common complications being increased vaginal discharge and erosion or ulceration of the vaginal wall. Although pessaries represent a common therapeutic modality, there are limited data regarding fitting and management (153). Even less is known about which type

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of pessary is better for enteroceles and rectoceles, although the site of prolapse does not appear to affect the ability to retain a pessary (154). Pessaries can be divided into subtypes of supportive and space occupying (155). Some of the space-occupying pessaries, such as the Gellhorn and cube, use a suction mechanism to maintain vaginal retention, whereas others, like the donut, do not. In theory, space-occupying pessaries and those that exert forces against the posterior wall and vaginal apex (donut, inverted Gehrung) should aid in treatment of rectoceles and enteroceles. However, there is a lack of data regarding the efficacy of pessaries for relieving symptoms of disordered defecation. One prospective study

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found that stage III–IV posterior vaginal wall prolapse was an independent predictor for discontinuation of pessary use in favor of surgical repair (156). More research is needed to determine the role of pessaries for treatment of rectoceles and enteroceles as well as symptoms that are likely to be improved using a pessary.

Table 25.8 Laxatives for the Treatment of Disordered Defecation

Type of Laxative	Adult Dose	Onset of Action	Side Effects
<i>Bulk-Forming Laxatives</i>			
Natural (<i>psyllium</i>)	7 g PO	12–72 h	Impaction above strictures
Synthetic (<i>methylcellulose</i>)	4–6 g PO	12–72 h	Fluid overload
<i>Emollient Laxatives</i>			
Docusate salts	50–500 mg PO	24–72 h	Skin rashes
Mineral oil	15–45 ml PO	6–8 h	Decreased vitamin absorption Lipid pneumonia
<i>Hyperosmolar Laxatives</i>			
<i>Polyethylene glycol</i>	3–22 L PO	1 h	Abdominal bloating
<i>Lactulose</i>	15–60 mL PO	24–48 h	Abdominal bloating
<i>Sorbitol</i>	120 mL 25% solution PO	24–48 h	Abdominal bloating
<i>Glycerine</i>	3 g suppository	15–60 min	Rectal irritation
	5–15 mL enema	15–30 min	Rectal irritation
<i>Saline Laxatives</i>			
<i>Magnesium sulfate</i>	15 g PO	0.5–3 h	Magnesium toxicity
<i>Magnesium phosphate</i>	10 g PO	0.5–3 h	
<i>Magnesium citrate</i>	200 mL PO	0.5–3 h	

<i>Stimulant Laxatives</i>			
Castor oil	15–60 mL PO	2–6 h	Nutrient malabsorption
<i>Diphenylmethanes</i>			
<i>Phenolphthalein</i>	60–100 mg PO	6–8 h	Skin rashes
Bisacodyl	30 mg PO	6–10 h	Gastric irritation
	10 mg PR	0.25–1 h	Rectal stimulation
<i>Anthraquinones</i>			
<i>Cascara sagrada</i>	1 mL PO	6–12 h	Melanosis coli
<i>Senna</i>	2 mL PO	6–12 h	Degeneration of Meissner and Auerbach plexuses
<i>Aloe (Casanthrol)</i>	250 mg PO	6–12 h	
<i>Danthron</i>	75–150 mg PO	6–12 h	Hepatotoxicity (w/docusate)

PO, by mouth; PR, per rectum.

From **Wald A**. Approach to the patient with constipation. In: **Yamada T**, ed. *Textbook of gastroenterology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1999:921, with permission.

Surgical Treatment

Following is a review of the efficacy of various surgical treatments for specific conditions associated with constipation and disordered defecation.

Slow Transit/Colonic Inertia

Subtotal colectomy with ileosigmoid or ileorectal anastomosis is considered by many to be the surgical treatment of choice for slow-transit constipation refractory to medical management.

Most surgeons restrict the use of this surgical procedure to the most extreme cases and typically operate on fewer than 10% of patients. Strict criteria for surgery include the following: chronic, severe, disabling symptoms unresponsive to medical therapy; slow transit in the proximal colon; no evidence of pseudo-obstruction; and normal anorectal function (144). Success rates are variable and depend on several factors. An extensive review of colectomy for slow-transit constipation analyzed 32 studies from 1981 to 1988 and found satisfaction rates ranged from 39% to 100% (157). Higher success rates occurred in studies in the United States (n = 11, median 94%, range 75%–100%) and prospective studies (n = 16, median 90%, range 50%–100%). Superior outcomes occurred in those who had a complete physiologic evaluation and proven slow-transit constipation. Patients with anismus had higher rates of recurrent symptoms and lower satisfaction levels (158). Poorer outcomes occurred with ileosigmoid and cecorectal anastomosis than with ileorectal anastomosis. Those with segmental resection (hemicolectomy) had the worst outcome. None of the studies had a comparison group, and outcomes were variable and lacking validated measures. Morbidity associated with the operation included small bowel obstruction (median 18%, range 2%–71%), need for reoperation (median 14%, range 0%–50%), diarrhea (median 14%, range 0%–46%), fecal incontinence (median 14%, range 0%–52%), recurrent constipation (median 9%, range 0%–33%), persistent abdominal pain

(median 41%, range 0%–90%), and permanent ileostomy (median 5%, range 0%–28%). Mortality ranged from 0%–6% (159). A quality-of-life study revealed that the score correlated poorly with frequency of bowel movements. However, a lower score was seen in those patients who had persistent abdominal pain, diarrhea, fecal incontinence, and permanent ileostomies. Overall satisfaction with the procedure was very high and correlated with the quality-of-life score (160).

Surgical alternatives to subtotal colectomy include ileostomy, cecostomy with antegrade continence enemas, and sacral nerve stimulation. Subtotal colectomy has never been directly compared with ileostomy, but those who had a permanent diversion after subtotal colectomy had lower quality-of-life scores. Patients undergoing cecostomy with antegrade continence enemas can expect to have satisfactory function approximately one half of the time, with most requiring additional revision procedures secondary to stomal complications (161). Although sacral nerve stimulation has primarily been used for fecal incontinence, the results of a few small studies evoke optimism for its use in chronic constipation and slow-transit constipation (130,162,163).

Pelvic Organ Prolapse

The variety of surgical treatment techniques for the repair of rectocele include posterior colporrhaphy, defect-directed repair, posterior fascial replacement, transanal repair, and abdominal repair with sacral colpopexy. When an enterocele is present, a culdoplasty usually is performed. In cases of perineal descent, abdominal sacral colpoperineopexy is the procedure of choice. Suture rectopexy can be performed in

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conjunction with sacral colpoperineopexy if rectal prolapse is present. Despite the routine use of these procedures, data are limited regarding symptomatic improvement of disordered defecation. Greater detail regarding the specific techniques for many of these procedures will be provided in Chapter 24. This section will focus on surgical outcomes, including anatomic cure of prolapse, improvement of defecatory dysfunction symptoms, and morbidity associated with the procedure.

Posterior Colporrhaphy

Posterior colporrhaphy has been the surgical procedure for rectocele repair preferred by gynecologic surgeons for more than 100 years. Traditional posterior colporrhaphy narrows the vaginal caliber through plication of the rectovaginal septum and usually includes a perineorrhaphy, which narrows the introitus. Despite its broad use, there is a paucity of data regarding long-term anatomic success, symptomatic improvement, and sexual function following the procedure. The outcomes of several studies are summarized in Table

25.9

(164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182).

Anatomic cure and relief of vaginal bulge occurred in 76% to 96% of patients. In these studies,

the procedure was ineffective at treating constipation, vaginal digitations (splinting), and fecal incontinence. Dyspareunia developed in 8% to 26% of patients with and without levator plication (164,165,166,167,168,183). As early as 1961, high rates of dyspareunia have been reported with this procedure in as many as 50% of patients (184).

Many feel that the successful anatomic support obtained with this procedure is offset by the modest relief of functional symptoms and high rate of *de novo* dyspareunia. However, a recent prospective case series of 38 women undergoing posterior colporrhaphy along with concomitant procedures for rectocele and obstructed defecation revealed markedly different results (185). Fascial plication was performed without levator plication, and perineal body reconstruction rather than routine perineorrhaphy was employed when indicated. Anatomic cure rate was 87% at 12 months and 79% at 24 months. Subjective cure rate was 97% at 12 months and 89% at 24 months. There was significant improvement in preoperative and postoperative symptoms for constipation (76% versus 24%), digitations (100% versus 16%), awareness of prolapse (100% versus 5%), obstructed defecation (100% versus 13%), and dyspareunia (37% versus 5%). There was no difference in fecal incontinence and only 1 case of *de novo* dyspareunia. The authors attribute their improved anatomic and functional outcomes and combined improvement in dyspareunia to exclusion of levator plication, perineorrhaphy, and excision of vaginal epithelium. An additional benefit may be derived during mobilization of the vaginal epithelium, when scar tissue from prior episiotomy or surgery is divided. They also found that preoperative defecating proctography was of limited value and have stopped its routine use as part of the preoperative evaluation for women with symptomatic rectoceles and obstructive defecation.

Defect-Directed Repair

The goal of a defect-directed repair or site-specific repair is to restore normal anatomy (30). This procedure can be combined with a perineal body reconstruction, if necessary, but usually does not routinely involve perineorrhaphy. Table 25.9 lists the anatomic and functional outcomes for this type of repair. **Anatomic cure rates range from 82% to 100%, which are similar to those for posterior colporrhaphy. This procedure also resulted in modest improvement for symptoms of difficult evacuation, vaginal bulge, and vaginal digitations, which appear to be slightly better than for posterior colporrhaphy** (169,170,171,172,173,183). Constipation symptoms significantly decreased in only one study (169). All studies reported low rates of *de novo* dyspareunia with good functional and anatomic outcomes, but the long-term durability of the procedure is unknown. All but one of these studies included concomitant prolapse and urinary incontinence procedures.

There are no randomized trials comparing posterior colporrhaphy with defect-directed repair. A retrospective (historical) cohort study of 307 patients with at least 1 year

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of post operative follow-up evaluated 124 women who underwent site-specific repair and 183 who underwent posterior colporrhaphy (186). The decision regarding the type of surgical repair

was made intraoperatively by the surgeon. If a discrete defect was identified, a site-specific repair was performed. Otherwise, posterior colporrhaphy was performed for cases with diffuse attenuation of the rectovaginal septum. Approximately 75% of patients in each group underwent perineorrhaphy for separation of the perineal muscles. **The recurrence rates for defect-directed repairs were more than double those for posterior colporrhaphy** (33% versus 14% for second degree, 11% versus 4% for third degree or greater respectively based on the Baden-Walker halfway system). Mean postoperative point Bp was -2.2 ± 0.3 vs. -2.7 ± 0.4 , respectively, based on the POP-Q system. There were no detectable differences in postoperative constipation and fecal incontinence between the two procedures. When comparing preoperative and postoperative outcomes, neither procedure improved symptoms of constipation (31% versus 35%), abdominal pain (11% versus 10%), or fecal incontinence (17% versus 19%). Dyspareunia was higher postoperatively (17% versus 8%, $p = 0.001$) with no difference between surgical techniques (16% versus 17%). The high rate of dyspareunia in the absence of levator plication is most likely attributed to the perineorrhaphy, which was commonly used in both groups. **Their outcomes must be interpreted with caution because of the large selection bias and lack of validated measures.** Differences in postoperative blood pressure measurements may be statistically significant but not necessarily clinically significant. The results are intriguing, but future randomized control trials are necessary to ultimately determine which procedure is optimal.

Table 25.9 Rectocele Repairs										
<i>Posterior Colporrhaphy</i>										
	<i>Arnold (164)</i>		<i>Mellgren (165)^a</i>		<i>Kahn (166)</i>		<i>Weber (167)^a</i>		<i>Sand (168)^a</i>	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
N	29		25	25	231	171	53	53	70	67
Follow-up (mean) months				12		42		12		12
Levator plication		Yes		Yes		Yes		No		No
Anatomical cure (%)		80		96		76				90
Constipation (%)	75	54	100	88	22	33				
Protrusion (%)			21	4	64	31				
Splinting/digitations (%)	20		50	0		33				
Fecal incontinence		36	8	8	4	11				
De novo dyspareunia^b (%)		23		8		16		26		
<i>Defect-Directed Repair</i>										
	<i>Cundiff (169)</i>		<i>Porter (170)</i>		<i>Kenton (171)</i>		<i>Glavind (172)</i>		<i>Singh (173)^a</i>	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
N	69	61	125	72	66	46	67	67	42	33

Follow-up (mean) months	12	6	12	3	18					
Anatomic cure	82	82	90	100	92					
Constipation (%)	46	13	60	50	41	57				
Difficult defecation	32	15	61	44	53	46	40	4	57	27
Protrusion (%)	100	18	38	14	86	9			78	7
Splinting/digitations (%)	39	25	24	14	30	15				
Fecal incontinence (%)	13	8	24	21	30				9	5
Dyspareunia (%)	29	19	67	46	28	8	12	3	31	15
De novo dyspareunia^b (%)	2		4		7			3		0
Repairs with Grafts										
	<i>Oster (174)</i>		<i>Sand (168)^a</i>		<i>Goh (175)^a</i>		<i>Kohli (176)</i>		<i>Mercer-Jones (177)^a</i>	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
<i>Graft route</i>	<i>Autologous Transvaginal</i>		<i>Polygalactin mesh Transvaginal</i>		<i>Polypropylene Transvaginal</i>		<i>Porcine dermis Transvaginal</i>		<i>Polypropylene Transperineal</i>	
N	15	15	73	65	43	43	43	30	22	22
Follow-up (mean) months		30		12	12			12		12
Anatomic cure		100		92		100		93		95
Constipation (%)		33							50	14
Difficult defecation	47	0							95	32
Protrusion (%)	80	0			100	0			86	23
Splinting/digitations (%)	100	12							64	23
Fecal incontinence (%)										5
Dyspareunia (%)		20								
Transanal Repair										
	<i>Sullivan (178)</i>		<i>Sehapavak (179)</i>		<i>Jenssen (180))^a</i>		<i>Van Dam (181)^{a,c}</i>		<i>Ayabaca (182)^a</i>	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
N	137	117	355	204	64	64	89	89	49	34
Follow-up (mean) months		18				12		52		48
Anatomic cure		96		98		70		72		90
Constipation (%)			82	15			63	33	83	32

Difficult defecation	58	2	72	16	92	27		
Protrusion (%)	27		38	3	40	28		
Splinting/ digitations (%)		26	26	4	23	0	38	
Fecal incontinence (%)	39	3	40	9	10	16	71	27
Dyspareunia (%)		0	20		28	44		
^a Prospective. ^b In sexually active patients. ^c Combined Transanal and Transvaginal Repair								

Transanal Repair

Transanal repair involves repair of the rectocele through a transanal incision with excision of redundant rectal mucosa and plication of the rectovaginal septum and rectal wall. The procedure was developed and is primarily used by colorectal surgeons to treat constipation or obstructed defecation associated with "low" or distal rectoceles. The advantages of this approach include excision of redundant rectal mucosa and the ability to treat other anorectal pathology, such as hemorrhoids or anterior rectal wall prolapse (187). Disadvantages include the inability to repair higher rectoceles, enteroceles, cystoceles, uterine prolapse, and defects in the perineal

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body or anal sphincter (188). Major complications of infection (6%) and rectovaginal fistula (3%) are relatively rare (179). Most studies did not require vaginal bulging or protrusion symptoms as a prerequisite for surgery. The results of several studies are summarized in Table 25.8. The anatomic cure rate was 70% to 98%, and symptoms of constipation, difficult evacuation, and vaginal digitations appear to improve (178,179,180,181,182,183).

Recent reviews have compared transanal with transvaginal rectocele repair using the results of two small, randomized control trials (189,190,191,192). Women with compromised sphincter function and other symptomatic prolapse were excluded. **The results for transvaginal repair were superior to those for transanal repair with respect to subjective failure rate** (relative risk [RR] 0.36, 95% CI 0.13 -1) and objective failure rate (RR 0.24, 95% CI 0.09-0.64) (189). In one study, a significant decrease occurred in the depth of rectocele on postoperative defecography for the transvaginal group compared with the transanal group (2.73 cm versus 4.13 cm, respectively) (192). The transvaginal group had fewer problems with bowel evacuation, but this finding was not statistically significant. In one study, researchers discovered that 38% of patients developed fecal incontinence following transanal repair (164). In the two randomized trials, no significant differences were seen in the rate of fecal incontinence or dyspareunia, but the studies were underpowered to detect a difference (191,192). **Although a vaginal approach has been considered superior to a transanal approach for rectocele repair, studies are retrospective and impossible**

to compare because the indications for transanal repairs are generally different from those for transvaginal repairs. A prospective, randomized trial with adequate power to evaluate symptomatic outcomes of bowel and sexual function along with anatomic cure is warranted.

Posterior Fascial Replacement

Rectocele repair with graft augmentation is becoming more common despite a paucity of supporting evidence indicating its benefits over standard procedures. The reason for its emergence is the theory that vaginal hernia repairs behave similar to abdominal hernia repairs, which have a documented decrease in recurrence when augmented with grafts. A variety of graft materials have been employed with posterior colporrhaphy and defect-directed repairs including autograft, allograft, xenograft, and synthetic mesh. There are no comparison data to aid in selecting the optimal graft. The purpose of the graft is debatable. It can either be intended to replace existing fascia as a permanent barrier or to provide an absorbable scaffold for collagen deposition, scar formation, and remodeling. The ideal material should have a low erosion rate, be relatively inexpensive, and decrease recurrence rates without causing bowel or sexual dysfunction. The outcomes for rectocele repair using graft materials placed either vaginally or abdominally appear in Table 25.9 (34,168,174,175,176,177,183,193,194), High anatomic cure rates of 89% to 100% occurred, and symptoms of constipation, difficult evacuation, and vaginal bulge also appeared to improve.

The largest prospective study and only randomized trial used absorbable vaginal mesh for rectocele repair (168). Patients were randomly assigned to fascial replacement with polyglactin 910 mesh at the time of anterior and posterior colporrhaphy. There were no differences in recurrence rates when comparing 70 women with a traditional colpoperineorrhaphy with 73 women having a traditional repair plus mesh: 10% versus 8% respectively. This study did not describe changes in bowel or sexual function, and there were no mesh-related adverse events. The risks of vaginal mesh erosion and severe complications may be relatively low but carry significant morbidity, including rectovaginal fistula, persistent vaginal bleeding and discharge, dyspareunia, and the need for additional surgery (175,183). **Nonsynthetic grafts appear to be safer, with fewer erosions compared with synthetic grafts.** Future prospective, randomized trials are under way to assess the effect of fascial replacement on symptoms of bowel and sexual function as well as long-term anatomic cure.

Abdominal Rectocele Repair

The abdominal approach to rectocele repair may be of value when a superior defect in the rectovaginal fascia occurs in a patient with accompanying enterocele, uterine prolapse, or vault prolapse. If a patient is undergoing an abdominal or laparoscopic procedure such as a sacral colpopexy, the graft can be extended along the posterior vaginal wall to correct proximal defects in the rectovaginal septum (195). There are limited data regarding the efficacy of abdominal rectocele repair. The indication for this procedure, as well as the need for additional vaginal repair of distal defects, often is

determined intraoperatively.

Sacral Colpoperineopexy for Perineal Descent

Sacral colpoperineopexy is a modification of sacral colpoperineopexy aimed at correction of apical prolapse combined with rectocele and perineal descent (34). A continuous graft is placed from the anterior longitudinal ligament of the sacrum down to the perineal body.

This procedure can be accomplished either through a total abdominal approach or a combined abdominal and vaginal procedure. **If performing a total abdominal approach, the rectovaginal space is opened, and the rectum is dissected off the posterior vaginal wall and rectovaginal septum toward the perineal body. The graft is then sutured to the perineal body or as close to it as possible.** A rectovaginal examination with the surgeon's nondominant hand facilitates this attachment by supporting the perineal body. The graft is secured to additional points along the posterior vaginal wall and apex, and sacral colpoperineopexy is completed in the usual fashion.

If performing a combined abdominal and vaginal approach, the graft is secured to the perineal body vaginally. The posterior vaginal wall is opened, and a defect-directed rectocele repair is performed. Sacral colpoperineopexy is accomplished in the usual fashion except that the vaginal dissection is opened superiorly, creating a window to the abdominal dissection. The graft can then be passed down from the abdominal field to the vaginal field and anchored inferiorly to the perineal body and laterally to the arcus tendineus fascia rectovaginalis. Alternatively, perineal body stitches can be placed vaginally and then retrieved abdominally once the rectovaginal space is entered from above. The sutures are then incorporated into the caudal portion of the graft. The idea behind the latter technique is to minimize graft exposure to the vagina, which theoretically will decrease vaginal erosion rates (Fig 25.8).

Short-term outcomes for 19 patients who underwent sacral colpoperineopexy indicated good anatomic results for apical and posterior support as well as for perineal descent (34). Complete cessation of defecatory dysfunction symptoms was accomplished in 66% of patients. In a report of outcomes for a slightly different variation of the sacral colpoperineopexy, the authors' technique involved attachment of Marlex mesh to the perineal body using a needle carrier (194). The failure rate was 25% and mesh erosion rate was 5% for 205 patients with up to 10-year follow-up. A study of Mersilene mesh erosion rates related to sacral colpoperineopexy and sacral colpoperineopexy (196). They noted similar erosion rates between sacral colpoperineopexy and colpoperineopexy when the vagina was not opened, 3.2% versus 4.5%, respectively. However, the erosion rate was 16% with vaginal suture placement and 40% when the mesh was placed vaginally. The use of nonsynthetic grafts such as dermal allograft and xenograft may help prevent high erosion rates. In a case series of 11 patients, researchers performed sigmoid resection (if indicated) and suture rectopexy in conjunction with sacral colpoperineopexy using Alloderm for women with coexistent rectal prolapse, perineal descent, and defecatory dysfunction. Early follow-up (12.5 ± 7.7 months) revealed excellent improvement of defecatory dysfunction symptoms and quality-of-life considerations, with an 82% cure of perineal descent (197). **Sacral colpoperineopexy appears to have value for a select group of patients**, but larger prospective series with long-term anatomic and symptomatic outcomes are necessary to evaluate the durability of this procedure.

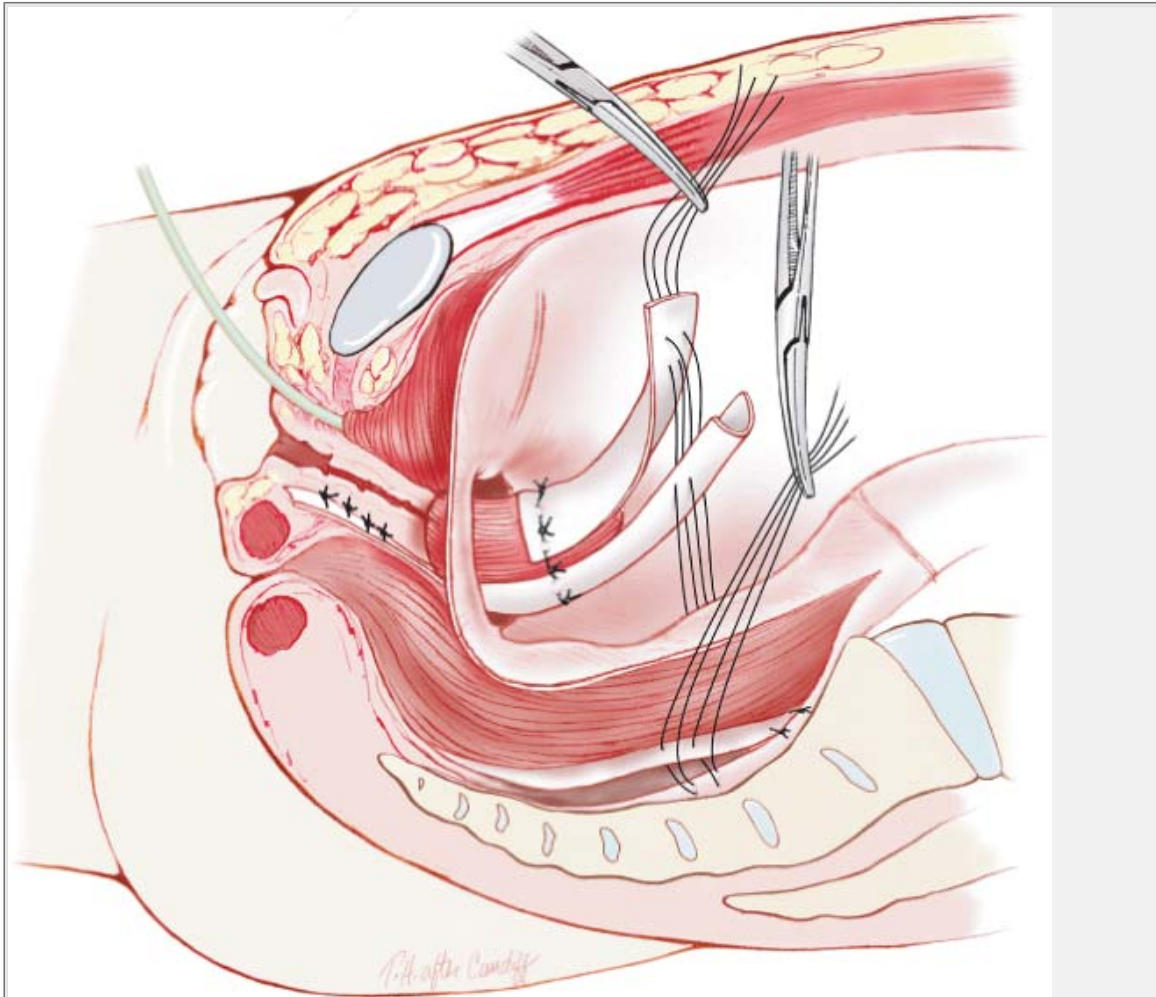


Figure 25.8 Abdominal sacral colpoperineopexy with sigmoid resection and suture rectopexy. This sagittal view shows the posterior graft sutured to the rectovaginal fascia and perineal body after defect-directed rectocele repair. The anterior graft is sutured to the pubocervical fascia. Both sheets will be secured to the sacral periosteum to the right of the rectum. Rectopexy sutures (*left*) have not yet been tied and secured. (Courtesy of Geoffrey W. Cundiff, M. D.).

Rectal Prolapse

Numerous surgical procedures have been described for the treatment of rectal prolapse and are broadly categorized into perineal or abdominal approaches. Most surgeons prefer an

abdominal procedure because of lower recurrence rates, reserving perineal procedures for more debilitated patients.

Abdominal Procedures

Abdominal procedures vary with respect to the extent of rectal mobilization, method of rectal fixation, and inclusion or exclusion of bowel resection. During abdominal rectopexy, the mesorectal plane is developed and the rectum mobilized down to the pelvic floor posteriorly, with care taken to identify and preserve the hypogastric nerves. Division of the lateral ligaments may or may not be performed. The concern is that division of the lateral ligaments will lead to rectal denervation and increased postoperative constipation. If performing a suture rectopexy, the fascia propria of the rectum is secured to the sacral periosteum from S-1 to S-3 (198). If performing a sigmoid resection with the rectopexy (Frykman-Goldberg resection rectopexy), the bowel resection is performed after mobilization and before suturing (199). The theoretical advantages of a rectosigmoid resection are creation of

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a dense area of fibrosis between the anastomotic suture line and the sacrum; removal of abundant rectosigmoid, avoiding torsion or volvulus; additional fixation through straightening of the left colon and decreased mobility from the phrenocolic ligament; and relief of constipation in select patients. It is typically reserved for patients with a long redundant sigmoid colon, although specific criteria have not been proposed. Mesh rectopexies are usually avoided because of concern for increased complications and infections associated with placement of a foreign body at the time of bowel resection. There are two basic types of mesh rectopexy: **posterior mesh rectopexy** and **anterior sling rectopexy (Ripstein procedure)** (200,201). A variety of materials have been used for this procedure, including absorbable and permanent mesh. The assumption is that placement of this material will provide increased support through increased fibrous tissue formation. During the Ripstein procedure, an anterior sling of fascia lata or synthetic mesh is placed in front of the rectum and sutured to the sacrum. Most surgeons avoid this procedure because of fear of obstructed defecation. Modifications using a posterolateral wrap have been developed to resolve this problem.

In a series of greater than 10 patients, there were five open series and five laparoscopic reports for suture rectopexy (202). The recurrence rates ranged between 0% and 9%. Most reports showed an improvement in fecal incontinence symptoms, but the results for constipation were variable. There were no mortalities noted and no difference between laparoscopic and open results. For posterior mesh rectopexy, there were 14 open series and five laparoscopic reports. The recurrence rates ranged between 0% and 6%. As with suture rectopexy, there was general improvement in fecal incontinence, mixed results for constipation, and no differences between laparoscopic and open outcomes. The mortality rate was between 0% and 3%, with increased rates of infection if resection rectopexy was performed. For anterior sling rectopexy (Ripstein procedure), there were eight studies with a recurrence rate between 0% and 12%. Again, there was a trend toward improvement of fecal incontinence and mixed response for constipation. Mortality ranged from 0% to 3%. For resection rectopexy (Frykman-Goldberg procedure), there were nine open series and three

laparoscopic reports. Recurrence ranged between 0% and 5%. There was general improvement in continence as well as an overall reduction in constipation observed in most studies. Mortality rate was 0% for all studies but one, in which it was 6.7% (203). This study was a small, randomized trial comparing 15 patients undergoing resection rectopexy to 15 patients undergoing absorbable mesh rectopexy. The patient who died was in the resection group and had a myocardial infarction. The authors concluded that sigmoid resection did not seem to increase operative morbidity but tended to diminish postoperative constipation, possibly by causing less outlet obstruction. The study was underpowered to detect a difference in morbidity or mortality.

The laparoscopic series demonstrated similar safety and efficacy to the open techniques, and the effect on continence and constipation tended to mirror the type of rectopexy performed. **In a small, randomized trial, there were significant short-term benefits with laparoscopic rectopexy compared with open rectopexy, including earlier ambulation, more rapid return to normal diet, shorter hospital stay, and lower morbidity** (204). Most surgeons believe that there are no differences in recurrence rates between suture and mesh rectopexy. Consequently, the role of mesh in these procedures is suspect. The role of division of the lateral ligaments is somewhat controversial. A Cochrane Review performed in 2000 concluded that division of the lateral ligaments was associated with less recurrent prolapse but more postoperative constipation (205). The authors acknowledged the limitations of their review, which consisted of very few trials with small sample sizes and methodological weakness. A review of seven open and four laparoscopic series involving division of the lateral ligaments revealed a general improvement in fecal incontinence and either no change or worsening of constipation (202). Conversely, there were 15 open and four laparoscopic series with preservation of the ligaments that displayed improved continence and a trend toward reduced constipation. This study suggests that preservation of the lateral ligaments is associated with an improvement in fecal incontinence and constipation symptoms.

Perineal Procedures

Perineal procedures are more easily tolerated because they avoid laparotomy. Thus, they are ideal for patients at high-risk for perioperative and postoperative morbidity and mortality. There are basically two perineal procedures: the *Delorme procedure* and *perineal rectosigmoidectomy* (Altemeier operation). Perianal encirclement procedures such as the Thiersch procedure are not recommended because of poor success rates, high recurrence rates, and fecal impaction.

The **Delorme procedure** was first described in 1900 and involves separation of the rectal mucosa from the sphincter and muscularis propria, followed by resection of the rectal mucosa, and plication of the distal rectal wall (muscularis propria) (206) (Fig. 25.9). A review of 10 series found a recurrence rate ranging between 4% and 38% and mortality rates of 0% to 4% (202). The low mortality rates are impressive considering a higher-risk population; however, the recurrence rates make it a less desirable procedure among healthy patients. There was a general improvement in fecal incontinence and constipation. Fecal incontinence

(presumably indicating anal sphincter disruption or denervation), chronic diarrhea, and severe perineal descent are associated with failure of this procedure (207). The Delorme operation may be preferred in cases when the prolapsing segment is shorter than 3 to 4 cm or there is no circumferential full-thickness prolapse, making perineal rectosigmoidectomy difficult to perform (202,208).

Perineal rectosigmoidectomy (Altemeier operation) has become the perineal procedure of choice (209). Among 12 studies, performance of full thickness excision of the rectosigmoid was associated with recurrence rates from 0% to 16% and mortality rates of 0% to 5%. Patients generally have minimal pain and a relatively uneventful postoperative course. Recurrent prolapse probably reflects inadequate resection. Incontinence results are modest at best but seem to improve substantially with the addition of levatorplasty. The addition of levatorplasty also appears to decrease the short-term recurrence rate (210), but there is no significant change in constipation with this procedure. Most agree that perineal rectosigmoidectomy with levatorplasty is the best procedure for very elderly patients and those with profound comorbidity. This is the preferred approach for patients with incarcerated, strangulated, or even gangrenous prolapsed rectal segment who are not candidates for abdominal rectopexy. Although there is a general consensus that abdominal rectopexy is better than perineal rectosigmoidectomy, there is

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only one small, prospective, randomized control trial comparing these procedures. This study did not have the power to detect a difference in recurrence rates but found that patients undergoing abdominal resection rectopexy had less fecal incontinence and better physiological results than patients who had perineal rectosigmoidectomy (205,211).



Figure 25.9 Delorme's procedure. After mucosal stripping to the full extent of the prolapse, the circular smooth muscle of the rectum is plicated. A mucosa-to-mucosa anastomosis is then performed.

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26

Puberty

Robert W. Rebar



- **Normal pubertal development occurs in a predictable orderly sequence over a definite time frame..**
- **The major causes of delayed puberty include anatomic genital tract abnormalities and hypo- and hypergonadotropic amenorrhea..**
- **When pubertal development occurs asynchronously, with development of breasts in the absence of significant pubic and axillary hair, the diagnosis is usually androgen insensitivity..**
- **The most common cause of precocious puberty is constitutional (idiopathic), but more serious causes must be ruled out and therapy geared toward optimizing adult height..**
- **The most common cause of heterosexual development at the expected age of puberty is polycystic ovary syndrome (PCOS)..**

***Puberty* is the period during which secondary sexual characteristics develop**

and the capability of sexual reproduction is attained. The physical changes accompanying pubertal development result directly or indirectly from maturation of the hypothalamus, stimulation of the sex organs, and secretion of sex steroids. Hormonally, puberty in humans is characterized by the resetting of the classic negative gonadal steroid feedback loop, alterations in circadian and ultradian (frequent) gonadotropin rhythms, and the acquisition in the woman of a positive estrogen feedback loop, which controls the monthly rhythm as an interdependent expression of gonadotropins and ovarian steroids.

The ability to evaluate and treat aberrations of pubertal development requires an understanding of the normal hormonal and physical changes that occur at puberty. An understanding of these changes is also important in evaluating young women with amenorrhea.

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Normal Pubertal Development

Factors Affecting Time of Onset

The major determinant of the timing of the onset of puberty is no doubt genetic, but a number of other factors appear to influence both the age at onset and the progression of pubertal development. Among these influences are nutritional state, general health, geographic location, exposure to light, and psychological state **(1)**. The concordance of the age of menarche in mother–daughter pairs and between sisters and in ethnic populations illustrates the importance of genetic factors (1). Typically, the age of menarche is earlier than average in children with moderate obesity (up to 30% above normal weight for age), whereas delayed menarche is common in those with severe malnutrition. Children who live in urban settings, closer to the equator, and at lower altitudes typically begin puberty earlier than those who live in rural areas, farther from the equator, and at higher elevations. Blind girls apparently undergo menarche earlier than sighted girls, suggesting some influence of light (2).

In Western Europe, the age of menarche declined 4 months each decade between 1850 and 1960 (1). Recent data suggest that the trend toward earlier pubertal development may be continuing among girls (but not boys) who live in the United States (3). It has been presumed that these changes represent improved nutritional status and healthier living conditions.

One of the more controversial hypotheses has centered on the role of total body weight and body composition on the age of menarche. It has been argued that a girl must reach a critical body weight (47.8 kg) before menarche can occur (4). More importantly, body fat must increase to 23.5% from the typical 16% of the prepubertal state, which presumably is influenced by nutritional status (5). This hypothesis is supported by observations that menarche occurs earliest in obese girls, followed by normal–weight girls, then underweight girls, and lastly anorectic girls (Fig. 26.1). The importance of other factors is indicated by observations that menarche is often delayed in morbidly obese girls, those with diabetes, and those who exercise intensely but are of normal body weight and body fat percentage. Moreover, girls with precocious puberty may undergo menarche even if they have a low body fat percentage, and other girls show no pubertal development with a body fat percentage of 27% (6). The hypothesis linking menarche to body weight and composition does not always seem valid because menarche is a late event in pubertal development.

Physical Changes during Puberty

The changes associated with puberty occur in an orderly sequence over a definite time frame. Any deviation from this sequence or time frame should be regarded as abnormal. Moreover, the pubertal changes, their relationships to each other, and the ages at which they occur are distinctly different in girls and in boys. Although this chapter focuses on girls, changes in boys are considered briefly as well.

Tanner Stage

In girls, pubertal development typically takes place over 4.5 years (Fig. 26.2).

Although generally the first sign of puberty is accelerated growth, breast budding is usually the first recognized pubertal change, followed by the appearance of pubic hair, peak growth velocity, and menarche. The stages initially described by Marshall and Tanner are often used to describe breast and pubic hair development (7).

With regard to breast development (Fig. 26.3), *Tanner stage 1* refers to the prepubertal state and includes no palpable breast tissue, with the areolae generally less than 2 cm in diameter. The nipples may be inverted, flat, or raised. In ***Tanner stage 2***, breast budding occurs, with a visible and palpable mound of breast tissue. The areolae begin to enlarge,

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the skin of the areolae thins, and the nipple develops to varying degrees. *Tanner stage 3* is reflected by further growth and elevation of the entire breast. When the individual is seated and viewed from the side, the nipple is generally at or above the midplane of breast tissue. In most girls, *Tanner stage 4* is defined by projection of the areola and papilla above the general breast contour in a secondary mound. Breast development is incomplete until *Tanner stage 5*, in which the breast is mature in contour and proportion. In most women, the nipple is more pigmented at this stage than earlier in development, and Montgomery's glands are visible around the circumference of the areola. The nipple is generally below the midplane of breast tissue when the woman is seated and viewed from the side. Full breast development usually occurs over 3 to 3.5 years, but it may occur in as little as 2

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years or not progress beyond stage 4 until the first pregnancy. Breast size is no indication of breast maturity.

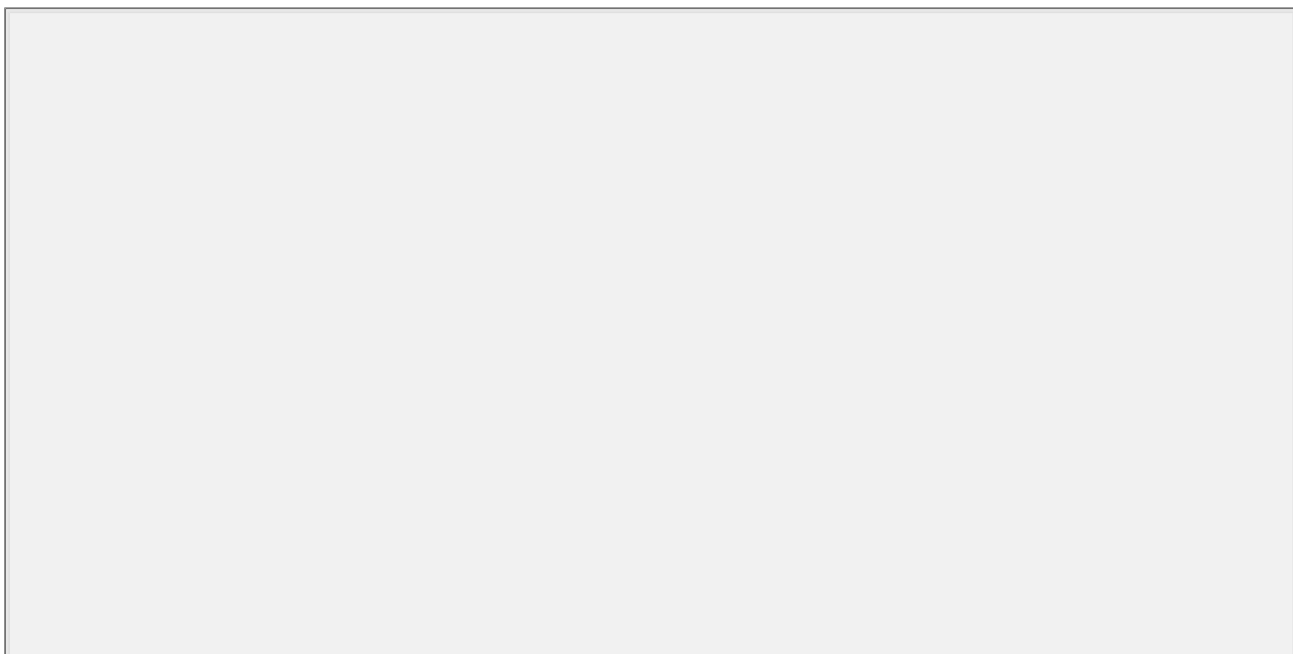




Figure 26.1 Normal twins at 12 years of age. The heavier twin (weighing 143 lb) is clearly more advanced in puberty than the lighter twin (weighing 87 lb). Anecdotal photographs and data such as these served to provide the basis for the theory that body fat, body mass, and menarche are linked. (From **Wilkins L.** *The diagnosis and treatment of endocrine disorders in childhood and adolescence.* 3rd ed. Springfield, IL: Charles C Thomas, 1965, with permission).

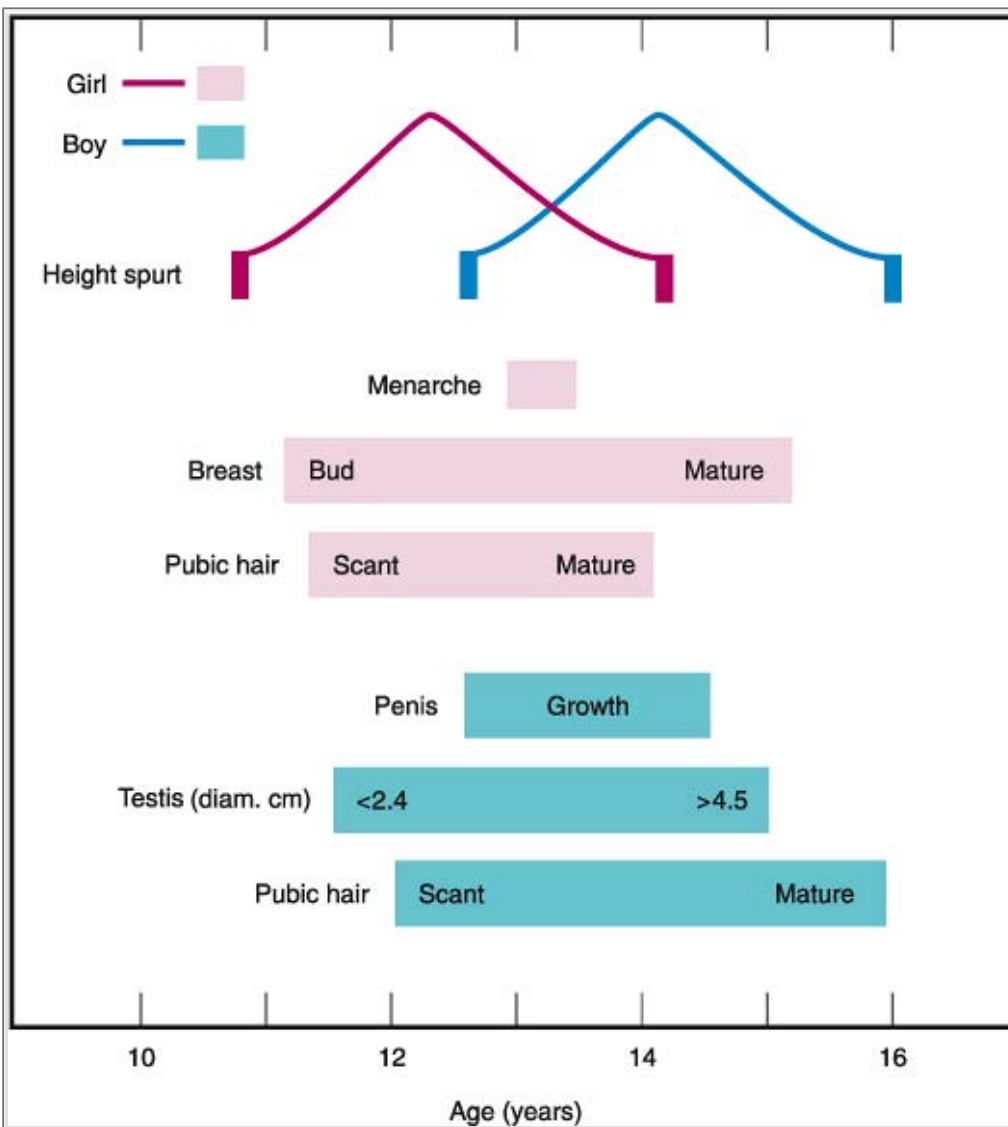


Figure 26.2 Schematic sequence of events at puberty. An idealized average girl and an idealized average boy are represented. (From **Rebar RW**. Practical evaluation of hormonal status. In: **Yen SSC, Jaffe RB**, eds. *Reproductive endocrinology: physiology, pathophysiology and clinical management*. 3rd ed. Philadelphia, PA: WB Saunders, 1991:830, with permission; based on data from **Marshall WA, Tanner JM**. Variations in patterns of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303, and **Marshall WA, Tanner JM**. Variation in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13–23, with permission.).

Pubic hair staging is related both to quantity and distribution (Fig. 26.4). In **Tanner stage 1**, there is no sexually stimulated pubic hair present, but some nonsexual hair may be present in the genital area. **Tanner stage 2** is characterized by the first appearance of coarse, long, crinkly pubic hair along the labia majora. In **Tanner stage 3**, coarse, curly hair extends onto the mons pubis. **Tanner stage 4** is characterized by adult hair in thickness and texture, but the hair is not distributed as widely as in adults and typically does not extend onto the inner aspects of the thighs. Except in certain ethnic groups, including Asians and American Indians, pubic hair extends onto the thighs in **Tanner stage 5**.

The staging of male pubertal sexual maturation is based on genital size and pubic hair development. **Tanner stage 1 is prepubertal**. **Tanner stage 2** of genital growth begins when testicular enlargement is first evident. Testis length along the longitudinal axis ranges from 2.5 to 3.2 cm. The size of the penis increases as well. Pigmented, curly pubic hair is first

visible around the base of the penis. In **Tanner stage 3**, there is further growth of the penis in both length and diameter, the scrotum develops further, and testis length increases to 3.3 to 4 cm. Thicker, curly hair extends above the penis. Tanner stage 4 involves further growth of the genitalia, with testis length ranging from 4 to 4.5 cm. Extension of pubic hair over the genital area continues, but the volume is less than in the adult. At this stage, the prostate gland is palpable by rectal examination. In **Tanner stage 5**, the genitalia are within the adult range in size. Stretched penile length measured along the dorsum averages 15.7 cm in adult men. Pubic hair spreads laterally onto the medial thighs. Hair may or may not extend from the pubic area toward the umbilicus and anus.

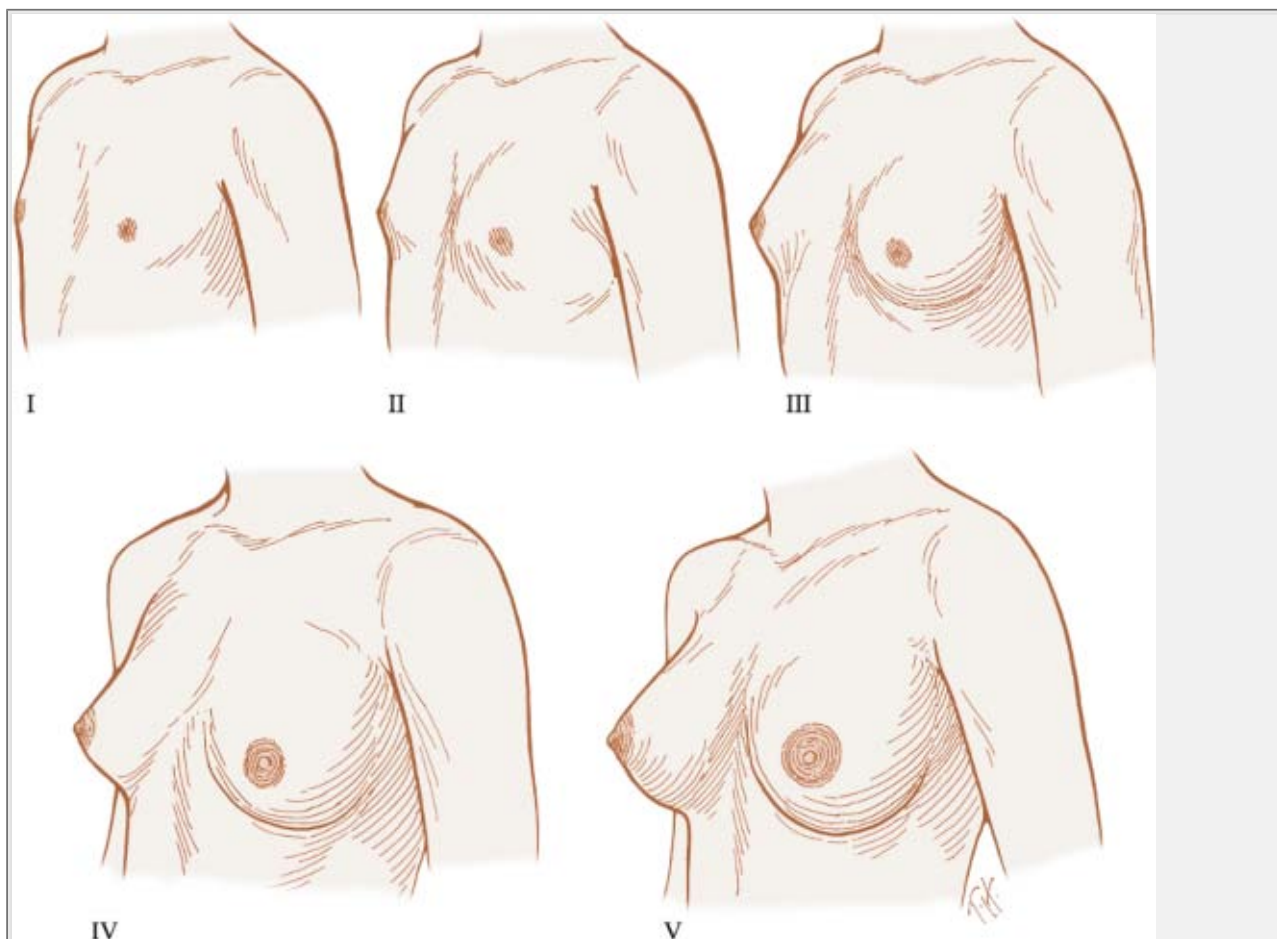


Figure 26.3 Diagrammatic depiction of Tanner breast stages in adolescent women. (From Ross GT, Van de Wiele RL, Frantz AG. *The ovaries and the breasts*. In: Williams RH, ed. *Textbook of endocrinology*. 6th edition. Philadelphia, PA: WB Saunders, 1981:355, with permission; adapted from Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. *Arch Dis Child* 1969; 44:291–303).

Pigmented pubic hair is often the first recognized sign of male puberty even though it typically occurs 6 months after genital growth begins. Tanner stage 3 puberty often is accompanied by symmetric or asymmetric gynecomastia, and mature sperm first can be identified with microscopic urinalysis.

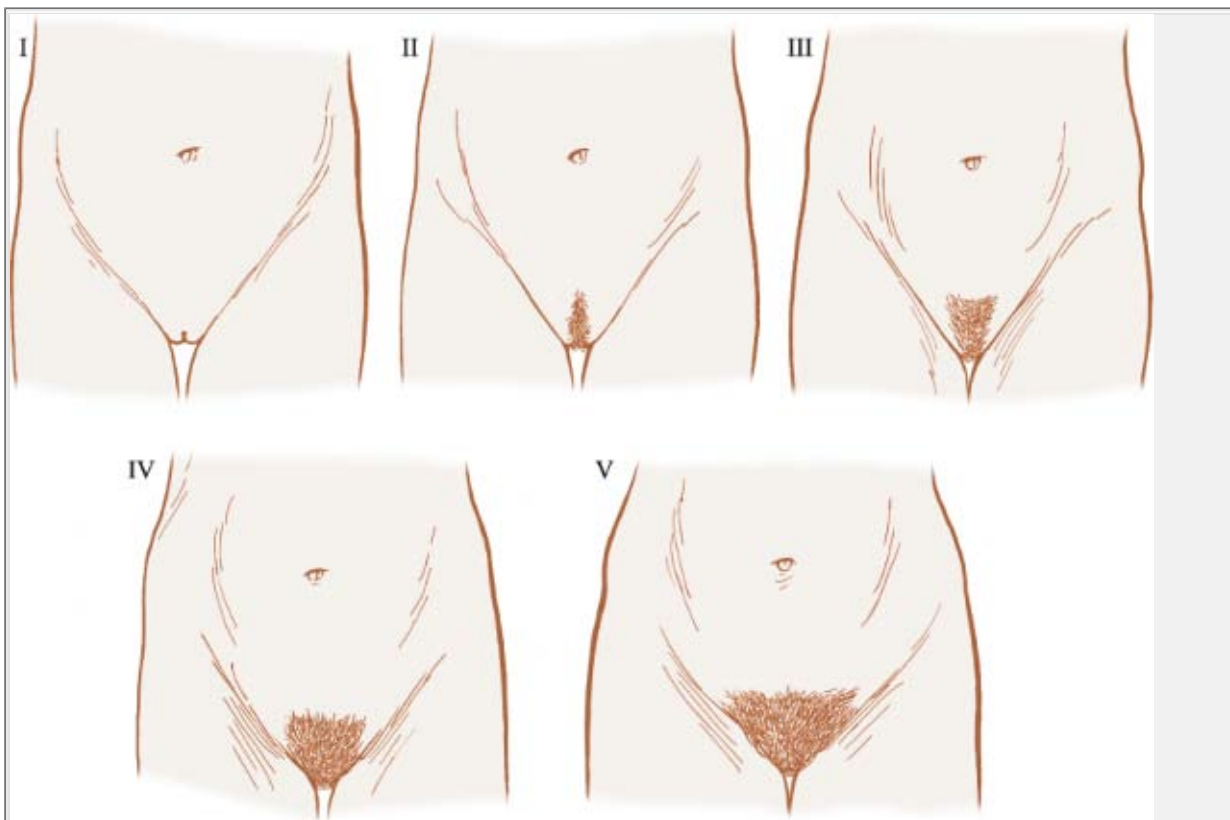


Figure 26.4 Diagrammatic depiction of Tanner pubic hair staging in adolescent women. (From Ross GT, VandeWiele RL, Frantz AG. The ovaries and the breasts. In: Williams RH, ed. *Textbook of endocrinology*. 6th ed. Philadelphia, PA: WB Saunders, 1981:355, with permission; adapted from Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303.)

Height and Growth Rate

Plotting height increments (i.e., growth velocity) against the phases of puberty allows one to see relationships during puberty (see Fig. 26.2). Girls reach peak height velocity early in puberty before menarche. As a consequence, they have limited growth potential after menarche. In contrast, boys reach peak height velocity about 2 years later than girls. Boys grow an average of 28 cm during the growth spurt, in comparison to a mean of 25 cm for girls. Adult men eventually are an average of 13 cm taller than adult women largely because they are taller at the onset of the growth spurt. Hormonal control of the pubertal growth spurt is complex. Growth hormone (GH), insulinlike growth factor 1 (IGF-1), and gonadal steroids play major roles. Adrenal androgens appear to be less important. Mutations limiting conversion of androgens to estrogens in males have confirmed that estrogen is the major stimulus to the pubertal growth spurt in both boys and girls (8).

During the growth spurt associated with puberty, the long bones in the body lengthen, and the epiphyses ultimately close. The bone or skeletal age of any individual can be estimated closely by comparing x-rays documenting the development of bones in the nondominant hand (most commonly), knee, or elbow to standards of maturation for the normal population. The Greulich and Pyle atlas is used most often for this purpose (9). Skeletal age is more closely correlated with pubertal stage than with chronologic age during puberty. **With height and chronologic age, an individual's bone age can be used to predict final adult height using the Bayley–Pinneau tables** (10).

Another practical clinical approach to predicting adult height uses midparental height. **The adjusted midparental height is calculated by adding 13 cm to the mother's height (for boys) or subtracting 13 cm from the father's height (for girls) and then determining the mean of the heights of the parents, including the adjusted height of the opposite-sex parent. Adding and subtracting 8.5 cm to the calculated predicted height approximates the target range of the third to the ninety-seventh percentile for the anticipated adult height of the child.** This quick calculation can be of assistance in evaluating individuals with delayed or precocious pubertal development and those with short stature.

Several changes in body composition also occur during pubertal development. **Although lean body mass, skeletal mass, and body fat are equal in prepubertal boys and girls, by maturity, men have 1.5 times the lean body mass and almost 1.5 times the skeletal mass of women, whereas women have twice as much body fat as men (1). The changes in body contour in girls, with accumulation of fat at the thighs, hips, and buttocks, occur during the pubertal growth spurt. In this regard, testosterone is a potent anabolic steroid and is responsible for the major changes in boys, whereas estrogen increases total body fat in a characteristic distribution at the thighs, buttocks, and abdomen in girls.**

Other physical changes show sexual dimorphism at puberty. In boys both the membranous and cartilaginous portions of the vocal cords lengthen much more than they do in girls, accounting for deepening of the voice. Comedones, acne, and seborrhea of the scalp begin because of increased secretion of adrenal and gonadal steroids at puberty. In general, early-onset acne correlates with the development of severe acne later in puberty. **The appearance of comedones in the nasal creases and behind the pinna may be the first indications of impending pubertal development.**

Hormonal Changes

By 10 weeks of gestation, gonadotropin-releasing hormone (GnRH) is present in the hypothalamus, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are present in the pituitary gland (11). Gonadotropin levels are elevated in both female and male fetuses before birth; the levels of FSH are higher in females. At birth, gonadotropin and sex steroid concentrations are still high, but the levels decline during the first several weeks of life and remain low during the prepubertal years. The hypothalamic-pituitary unit appears to be suppressed by the extremely low levels of gonadal steroids present in childhood.

Gonadal suppression of gonadotropin secretion is demonstrated by higher gonadotropin levels in children with gonadal dysgenesis and those who undergo gonadectomy before puberty (12).

Several of the hormonal changes associated with pubertal development begin before any of the physical changes are obvious. Early in puberty, there is increased sensitivity of LH to GnRH. Sleep-entrained increases in both LH and FSH can be documented early in puberty (13). In boys, the nocturnal increases in gonadotropin levels are accompanied by simultaneous increases in circulating testosterone levels (14). In contrast, in girls, the nighttime increases in circulating gonadotropin levels are followed by increased secretion of estradiol the next day (15) (Fig. 26.5). This delay in estradiol secretion is believed to be due to the additional synthetic steps required in the aromatization of estrogens from androgens. Basal levels of both FSH and LH increase through puberty. The patterns differ in boys and girls, with LH levels (measured in mIU/mL) eventually becoming greater than FSH levels (16) (Fig. 26.6). Although it now appears that gonadotropins are always secreted in an episodic or pulsatile fashion, even before puberty, the pulsatile secretion of gonadotropins is more easily documented as puberty progresses and basal levels increase (17).

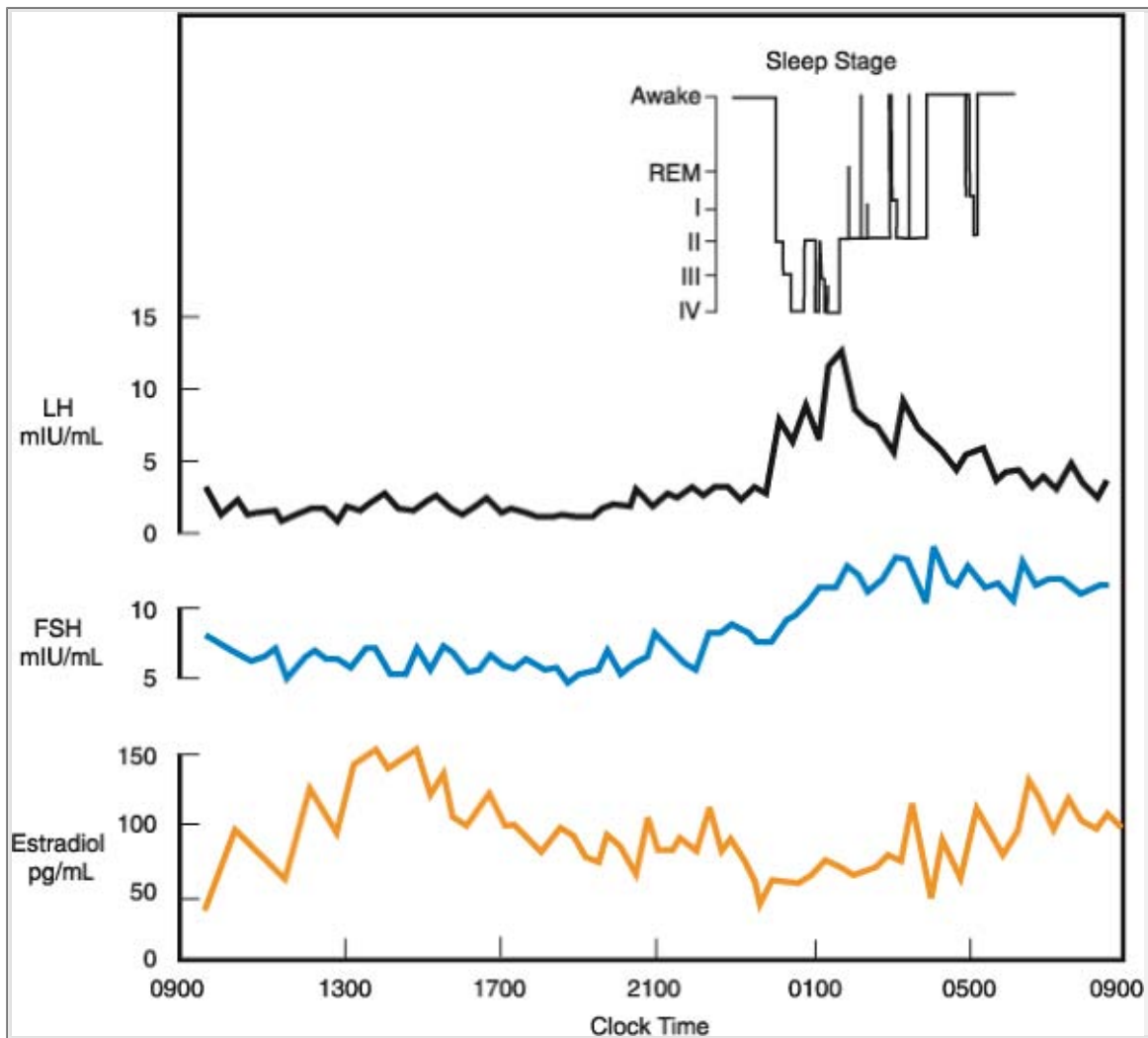


Figure 26.5 Patterns of circulating luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol in a stage 3 pubertal girl over a 24-hour period with the encephalographic stage of sleep indicated. (From Boyar RM, Wu RHK, Roffwarg H, et al. Human puberty: 24-hour estradiol patterns in pubertal girls. *J Clin Endocrinol Metab* 1976; 43: 1418–1421, with permission.)

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Increased adrenal androgen secretion is important in stimulating adrenarche, the appearance of pubic and axillary hair, in both boys and girls. Pubarche specifically refers to the appearance of pubic hair. Progressive increases in circulating levels of the major adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), begin as early as 2 years of age, accelerate at 7 to 8 years of age, and continue until 13 to 15 years of age (18,19,20). The accelerated increases in adrenal androgens begin about 2 years before the increases in gonadotropin and gonadal sex steroid secretion when the hypothalamic-pituitary-gonadal unit is still functioning at a low prepubertal level.

In girls, estradiol, secreted predominantly by the ovaries, increases steadily during puberty (16). Although, as noted, increases in estradiol first appear during the daytime hours, basal levels eventually increase during both the day and night. Estrone, which is secreted in part by the ovaries and arises in part from extraglandular conversion of estradiol and androstenedione, also increases early in puberty but plateaus by midpuberty. Thus, **the ratio of estrone to estradiol decreases throughout puberty, indicating that ovarian production of estradiol becomes increasingly important and peripheral conversion**

of androgens to estrone becomes less important during maturation..

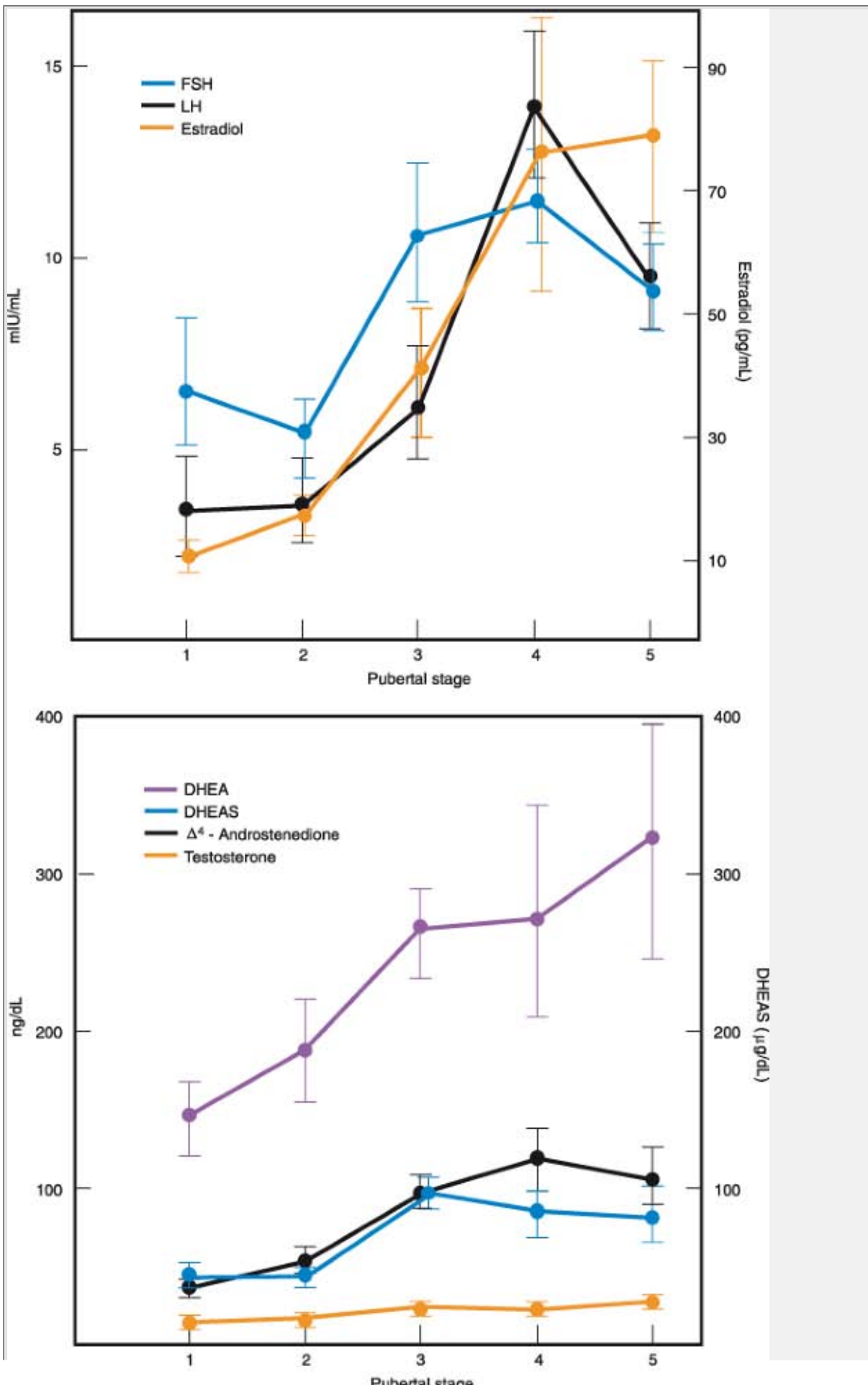


Figure 26.6 Increases (\pm standard error) in circulating levels of gonadotropins and adrenal and gonadal steroids through puberty in girls. DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate. (From **Emans SJH, Goldstein DP**. The physiology of puberty. In: **Emans SJH, Goldstein DP**, eds. *Pediatric and adolescent gynecology*. 3rd ed. Boston, MA: Little, Brown, 1990:95, with permission.).

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In boys, most of the testosterone in the circulation arises from direct secretion by the Leydig cells of the testis. Testosterone induces development of a male body habitus and voice change, whereas dihydrotestosterone (DHT), produced following 5 α reduction within target cells, induces enlargement of the penis and prostate gland, beard growth, and temporal hair recession during puberty. Mean plasma testosterone levels rise progressively during puberty, with the greatest increase occurring during Tanner stage 2 (21).

Growth hormone secretion increases along with increased gonadotropin secretion at the onset of puberty. It is believed that the increase in GH is mediated by estrogen, which in boys is dependent on aromatization of testosterone to estradiol and reflects increasing sex steroid production at puberty. Nonetheless, there are profound sex differences in GH secretion during puberty. Girls have higher basal levels of GH throughout puberty, reaching maximal levels around the time of menarche and decreasing thereafter. In contrast, basal concentrations of GH remain constant throughout puberty in boys. Growth hormone secretion is highly pulsatile, with most pulses occurring during sleep and with sex steroids increasing pulse amplitude rather than altering pulse frequency.

Growth hormone stimulates production of insulinlike growth factor 1 (IGF-1) in all tissues, with concentrations found in the circulation spilling over from the liver. During puberty the negative feedback effect of IGF-1 on GH secretion must be reduced because both IGF-1 and GH levels are high. Growth hormone and IGF-1 no doubt play significant roles in the changes in body composition that occur at puberty because both hormones are potent anabolic agents.

In the final stages of puberty in both boys and girls, GH secretion begins to diminish, returning to prepubertal levels in adult life, despite continued exposure to high levels of gonadal steroids.

Mechanisms Underlying Puberty

The mechanisms responsible for the numerous hormonal changes that occur during puberty are poorly understood, although it is recognized that a "central nervous system program" must be responsible for initiating puberty. It appears that the hypothalamic-pituitary-gonadal axis in girls develops in two distinct stages during puberty. First, sensitivity to the negative or inhibitory effects of the low levels of circulating sex steroids present in childhood decreases early in puberty. Second, late in puberty, there is maturation of the positive or stimulatory feedback response to estrogen, which is responsible for the ovulatory midcycle surge of LH.

Current evidence suggests that the central nervous system inhibits the onset of puberty until the appropriate time (22). Based on this theory, the neuroendocrine control of puberty is mediated by GnRH-secreting neurons in the medial basal hypothalamus, which together act as an endogenous pulse generator. At puberty, the GnRH pulse generator is reactivated (i.e., disinhibited), leading to increased amplitude and frequency of GnRH pulses. In turn, the increased GnRH secretion results in increased gonadotropin and then gonadal

steroid secretion. What causes this "disinhibition" of GnRH release is unknown.

The relationship between body mass and the onset of puberty has focused attention on leptin, produced by adipocytes, as a candidate for the factor initiating puberty. In the infertile leptin-deficient mouse, leptin therapy can induce sexual maturation and maintain fertility. Observations of two patients with leptin receptor mutations who failed to enter puberty suggest that leptin may have a similar role in humans.

Longitudinal studies of leptin secretion have noted that there is increased leptin secretion around the time of pubertal onset. Leptin levels are increased throughout puberty in girls but not in boys. Thus, it is not clear how important leptin is to pubertal development.

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Aberrations of Pubertal Development

Classification

Several aberrations of pubertal development, as detailed in Table 26.1, can occur in girls.

Pubertal aberrations can be classified in four broad categories:

- ***Delayed or interrupted puberty exists in girls who fail to develop any secondary sex characteristics by age 13, have not had menarche by age 16, or have not attained menarche 5 or more years since the onset of pubertal development..***

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- ***Asynchronous pubertal development is characterized by pubertal development that deviates from the normal pattern of puberty..***

- ***Precocious puberty has been defined as pubertal development beginning before the age of 7 years in white girls and before the age of 6 years in African American girls (3).*** This new definition is controversial and has been challenged because some feel that evaluation for breast or pubic hair development before 9 or 8 years of age in white or African American girls, respectively, may be warranted (23). It is clear that, in most cases, development nearer to the mean age of puberty is less likely to have a pathologic basis. Precocious pubertal development is characterized in several ways. In *isosexual* precocious puberty, the early changes are common to the phenotypic sex of the individual. In *heterosexual* precocious puberty, the development is characteristic of the opposite sex. Precocious puberty is sometimes termed "true" when it is of central origin with activation of the hypothalamic-pituitary unit. In precocious pseudopuberty, also known as *precocious puberty of peripheral origin*, secretion of hormones in the periphery (commonly by neoplasms) stimulates pubertal development.

- ***Heterosexual puberty is characterized by a pattern of development that is typical of the opposite sex occurring at the expected age of normal puberty..***

Table 26.1 Aberrations of Pubertal Development

I. Delayed or interrupted puberty**A. Anatomic abnormalities of the genital outflow tract**

1. Müllerian dysgenesis (Rokitansky-Küster-Hauser syndrome)
2. Distal genital tract obstruction
 - a. Imperforate hymen
 - b. Transverse vaginal septum

B. Hypergonadotropic (follicle-stimulating hormone >30 mIU/mL) hypogonadism (gonadal "failure")

1. Gonadal dysgenesis with stigmata of Turner syndrome
2. Pure gonadal dysgenesis
 - a. 46,XX
 - b. 46,XY
3. Early gonadal "failure" with apparent normal ovarian development

C. Hypogonadotropic (luteinizing hormone and follicle-stimulating hormone <10 mIU/mL) hypogonadism

1. Constitutional delay
2. Isolated gonadotropin deficiency
 - a. Associated with midline defects (Kallmann syndrome)
 - b. Independent of associated disorders
 - c. Prader-Labhart-Willi syndrome
 - d. Laurence-Moon-Bardet-Biedl syndrome
 - e. Many other rare syndromes
3. Associated with multiple hormone deficiencies
4. Neoplasms of the hypothalamic-pituitary area
 - a. Craniopharyngiomas
 - b. Pituitary adenomas
 - c. Other
5. Infiltrative processes (Langerhans cell-type histiocytosis)
6. After irradiation of the central nervous system
7. Severe chronic illnesses with malnutrition
8. Anorexia nervosa and related disorders
9. Severe hypothalamic amenorrhea (rare)
10. Antidopaminergic and gonadotropin-releasing hormone-inhibiting drugs (especially psychotropic agents, opiates)
11. Primary hypothyroidism
12. Cushing syndrome
13. Use of chemotherapeutic (especially alkylating) agents

II. Asynchronous pubertal development**A. Complete androgen insensitivity syndrome (testicular feminization)****B. Incomplete androgen insensitivity syndrome****III. Precocious puberty****A. Central (true) precocious puberty**

1. Constitutional (idiopathic) precocious puberty
2. Hypothalamic neoplasms (most commonly hamartomas)
3. Congenital malformations
4. Infiltrative processes (Langerhans cell-type histiocytosis)

5. After irradiation
6. Trauma
7. Infection
B. Precocious puberty of peripheral origin (precocious pseudopuberty)
1. Gonadotropin-secreting neoplasms
a. Human chorionic gonadotropin secreting
i. Ectopic germinomas (pinealomas)
ii. Choriocarcinomas
iii. Teratomas
iv. Hepatoblastomas
b. Luteinizing hormone-secreting (pituitary adenomas)
2. Gonadal neoplasms
a. Estrogen-secreting
i. Granulosa-theca cell tumors
ii. Gonadal sex-cord tumors
b. Androgen-secreting
i. Arrhenoblastomas
ii. Teratomas
3. Congenital adrenal hyperplasia
a. 21-Hydroxylase (P450c21) deficiency
b. 11 β -Hydroxylase (P450c11) deficiency
c. 3 β -Hydroxysteroid dehydrogenase deficiency
4. Adrenal neoplasms
a. Adenomas
b. Carcinomas
5. Autonomous gonadal hypersecretion
a. Cysts
b. McCune-Albright syndrome
6. Iatrogenic ingestion/absorption of estrogens or androgens
IV. Heterosexual puberty
A. Polycystic ovarian syndrome
B. Nonclassic forms of congenital adrenal hyperplasia
C. Idiopathic hirsutism
D. Mixed gonadal dysgenesis
E. Rare forms of male pseudohermaphroditism (Reifenstein syndrome, 5α-reductase deficiency)
F. Cushing syndrome (rare)
G. Androgen-secreting neoplasms (rare)

Disorders of sexual development and amenorrhea may be considered in relation to this classification of the aberrations of puberty. It is very helpful to document the growth of the individual and to plot the individual's height and weight on one of several commonly available growth charts (Fig. 26.7).

Delayed or Interrupted Puberty

The history and physical examination, with particular attention to growth, are most important in the evaluation of individuals with delayed puberty. Pubertal delay is

much more common in boys than in girls. It is important to remember that puberty may be delayed in any child suffering from any severe chronic disease, including celiac disease, Crohn disease, sickle cell anemia, and cystic fibrosis. Thus, chronic illness should be excluded during the history and physical examination. One possible approach to evaluation is depicted in Figure 26.8.

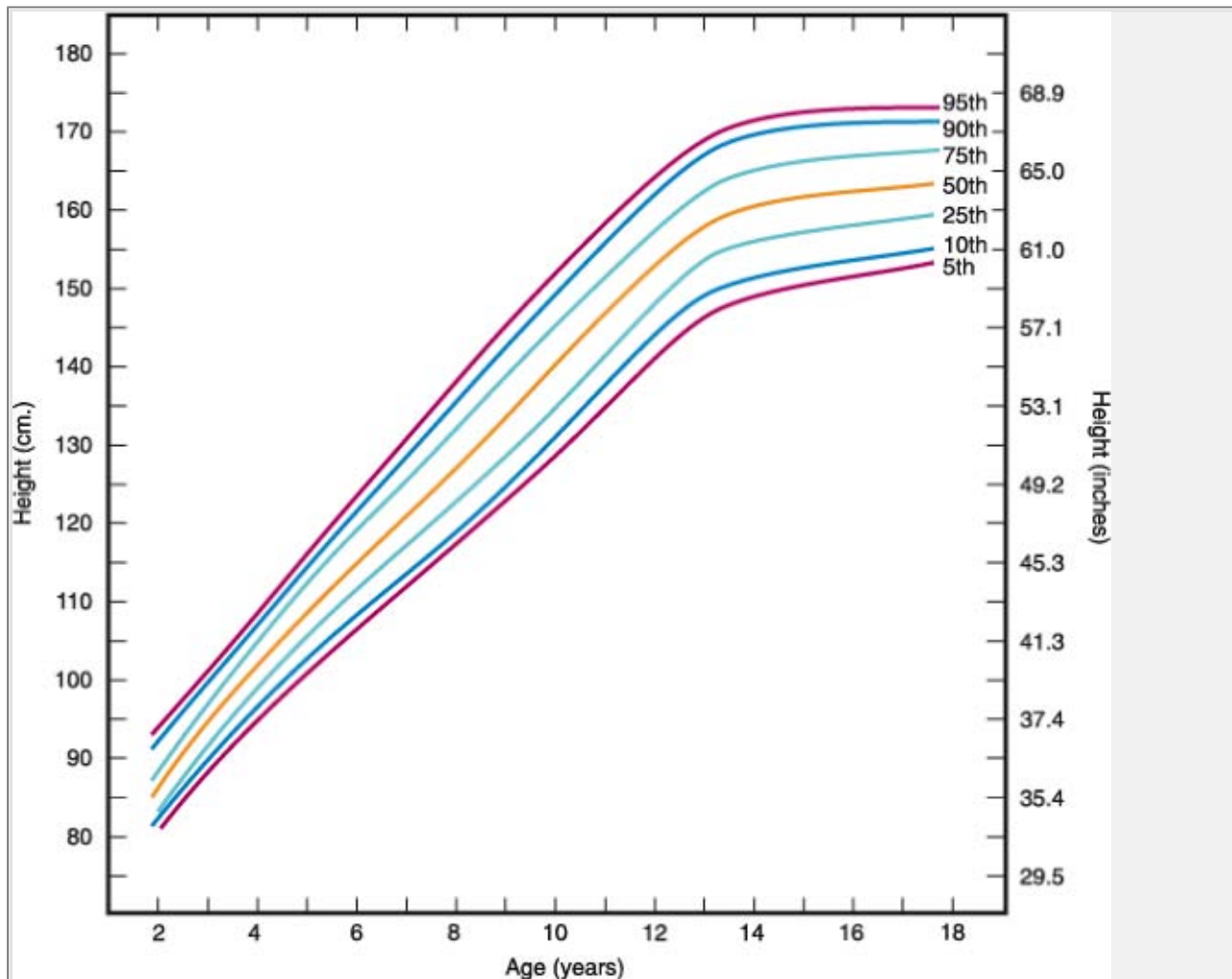


Figure 26.7 Growth chart showing stature by age percentiles for girls aged 2 to 18 years.

Weight can be plotted in a similar fashion. Several excellent growth charts are available to clinicians, including those from Ross Laboratories (Columbus, OH), Serono Laboratories (Randolph, MA), and Genentech, Inc. (South San Francisco, CA). (From **Hamill PVV, Drizd TA, Johnson CL, et al.**

Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr*

1979; 32: 607–629, with permission; based on data from the National Center for Health Statistics.)

Anatomic Abnormalities of the Genital Outflow Tract

Those girls who have mature secondary sex characteristics and any of a number of disorders of the outflow tract and uterus, often termed müllerian agenesis and dysgenesis, are most often identified on examination (Fig. 26.9). One of the most logical classification schemes that has been proposed is shown in Table 26.2 (24). The incidence of these anomalies was estimated to be 0.02% of the female population several years ago (25), but the incidence may have increased as a result of the maternal ingestion of diethylstilbestrol (DES) and the resultant increase in anomalies of the lumen of the uterus (class VI) (26). Of

the disorders unrelated to drug use, the septate uterus (class V) is most common.

Disorders of the outflow tract and uterus often occur as a part of a syndrome of malformations that include abnormalities of the skeletal and renal systems (*Rokitansky-Küster-Hauser syndrome*). Familial aggregates of the most common disorders of müllerian differentiation in girls—müllerian aplasia and incomplete müllerian fusion—are best explained on the basis of polygenic and multifactorial inheritance (27). It is clear that the *HOX* genes, a family of regulatory genes that encode for transcription factors, are essential for proper development of the müllerian tract in the embryonic period (28), and *HOXA 13* has been found to be altered in hand-foot-genital syndrome.

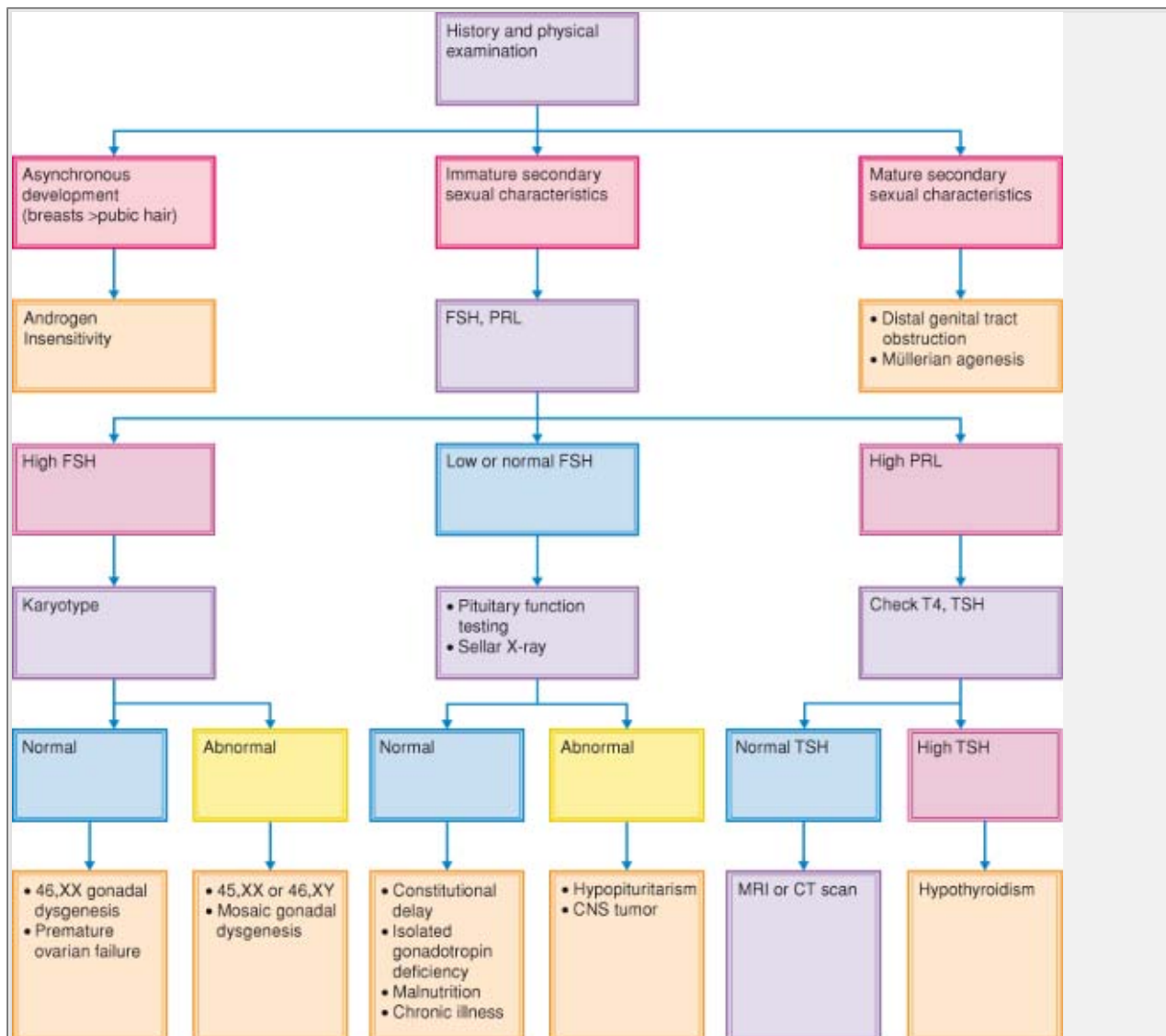


Figure 26.8 Flow diagram for the evaluation of delayed or interrupted pubertal development, including primary amenorrhea, in phenotypic girls. Girls with asynchronous development often present because of failure to menstruate. FSH, follicle-stimulating hormone; PRL, prolactin; T4, thyroxine; TSH, thyroid-stimulating hormone; CNS, central nervous system; MRI, magnetic resonance imaging; CT, computed tomography. (From **Rebar RW**. Normal and abnormal sexual differentiation and pubertal development. In: **Moore TR, Reiter RC, Rebar RW, et al**, eds. *Gynecology and obstetrics: a longitudinal approach*. New York, NY: Churchill Livingstone, 1993:97–133.).

The most common single anatomic disorder of puberty is the imperforate hymen, which prevents the passage of endometrial tissue and blood. These products can accumulate in the vagina (*hydrocolpos*) or uterus (*hydrometrocolpos*) and result in a bulging hymen that is often bluish in color. The affected individual often has a history of vague abdominal pain with approximately monthly exacerbations. It is sometimes difficult to distinguish an imperforate hymen from a transverse vaginal septum, and in most situations, examination under anesthesia is required.

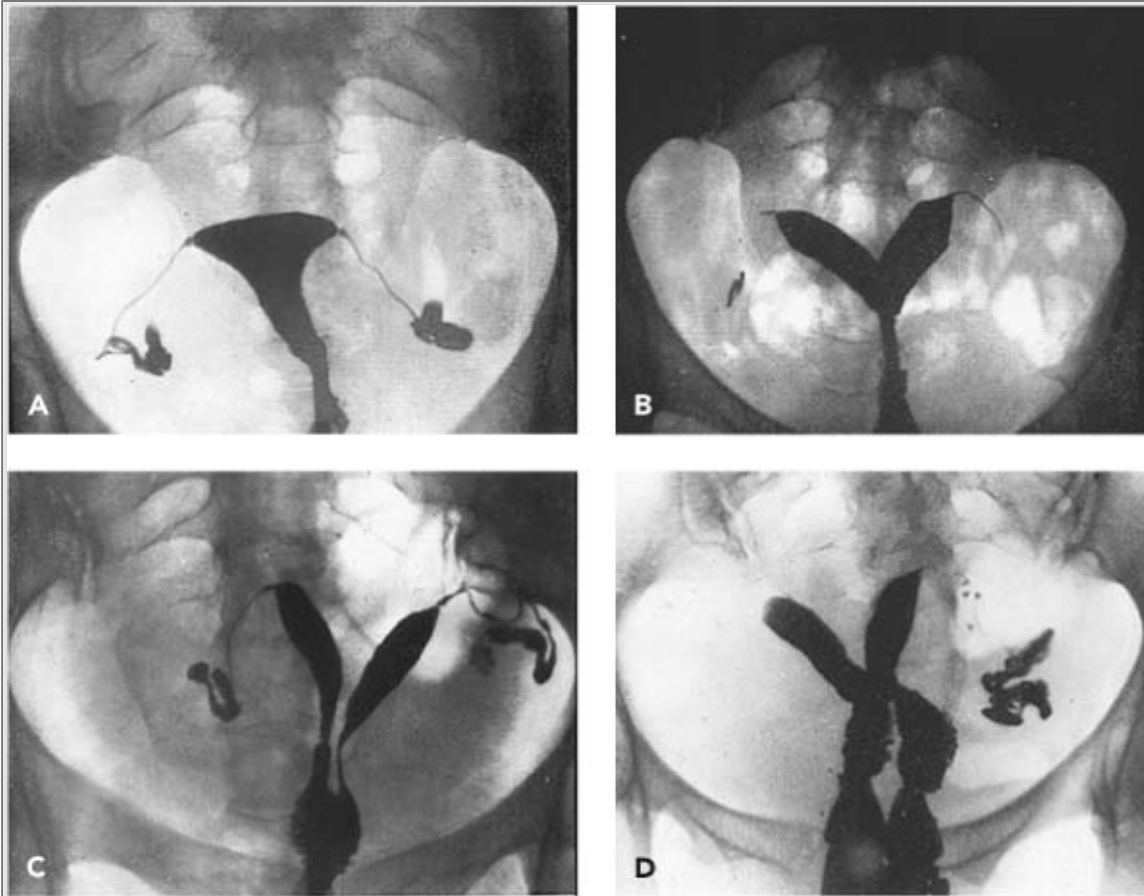


Figure 26.9 Hysterosalpingograms of normal and abnormal female genital tracts.

The radiographic photographs have been reversed to accentuate the uterine cavities. **A:** Normal study with bilateral spill. **B:** Bicornuate uterus. **C:** Uterus didelphis. **D:** Uterus didelphis with double vagina. (Courtesy of **Dr. A. Gerbie**; from **Spitzer IB, Rebar RW**. *Counselling for women with medical problems: ovary and reproductive organs*. In: **Hollingsworth D, Resnik R**, eds. *Medical counselling before pregnancy*. New York, NY: Churchill Livingstone, 1988:213–248, with permission.).

Regardless of the cause, uterine anomalies not involving segmental müllerian agenesis or hypoplasia (class I) are compatible with normal pregnancy. However, increased fetal wastage has been reported in the presence of these anomalies (29). Uterine malformations have been associated with spontaneous abortion, preterm labor, abnormal presentations, and complications of labor (i.e., retained placenta). Many of these uterine anomalies can be identified with hysterosalpingography (see Fig. 26.9). Hysterosalpingography, laparoscopy, and hysteroscopy have been used to differentiate a septate uterus (class V) from a bicornuate uterus (class IV). It is now clear that magnetic resonance imaging (MRI) and endovaginal ultrasonography (sometimes with sonohysterography) are as accurate as these invasive techniques in identifying the

abnormality (30).

Obstruction or malformation of the distal genital tract must be distinguished from androgen insensitivity. Individuals with androgen insensitivity have breast development in the absence of significant pubic and axillary hair development; the vagina may be absent or foreshortened in these women.

Hypergonadotropic and Hypogonadotropic Hypogonadism

Basal levels of FSH and prolactin should be determined in individuals in whom secondary sex characteristics have not developed to maturity (see Fig. 26.8). Bone age should be estimated from x-rays of the nondominant hand. If prolactin levels are elevated, thyroid function should be assessed to determine whether the individual has primary hypothyroidism. Paradoxically, primary hypothyroidism can result in precocious puberty

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as well. If thyroid function is normal, a hypothalamic or pituitary neoplasm is possible, and careful evaluation of the hypothalamic and pituitary area by MRI or computed tomography (CT) is indicated.

Table 26.2 Classification of Müllerian Anomalies

<i>Class I. Segmented müllerian agenesis or hypoplasia</i>
A. Vaginal
B. Cervical
C. Fundal
D. Tubal
E. Combined
<i>Class II. Unicornuate uterus</i>
A. With a rudimentary horn
1. With a communicating endometrial cavity
2. With a noncommunicating cavity
3. With no cavity
B. Without any rudimentary horn
<i>Class III. Uterus didelphys</i>
<i>Class IV. Bicornuate uterus</i>
A. Complete to the internal os
B. Partial
C. Arcuate
<i>Class V. Septate uterus</i>
A. With a complete septum
B. With an incomplete septum
<i>Class VI. Uterus with internal luminal changes</i>
Adapted from Buttrarm VC Jr, Gibbons WE. Müllerian anomalies: a proposed classification (an analysis of 144 cases). <i>Fertil Steril</i> 1979;32:40, with permission.

The karyotype should be determined in any individual with delayed puberty and increased basal FSH concentrations. Regardless of the karyotype, the individual with hypergonadotropic hypogonadism has some form of ovarian "failure," (i.e., primary hypogonadism).

Forms of Gonadal Failure

Turner Syndrome

Most affected individuals have a 45,X karyotype and Turner syndrome; still others have mosaic karyotypes (i.e., 45,X/46,XX; 45,X/46,XY) and may present with the Turner phenotype as well. Intrauterine growth restriction is common in infants with a 45,X karyotype. After birth, these patients generally grow slowly, beginning in the second or third year of life. They typically have many of the associated stigmata, including lymphedema and sometimes large cystic hygromas of the neck at birth; a webbed neck; multiple pigmented nevi; disorders of the heart, kidneys (most commonly horseshoe), and great vessels (most commonly coarctation of the aorta); and small hyperconvex fingernails (31) (Fig. 26.10). Diabetes mellitus, thyroid disorders, essential hypertension, and other autoimmune disorders are often present in individuals

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with 45,X karyotypes. Most 45,X patients have normal intelligence, but many affected individuals have an unusual cognitive defect characterized by an inability to appreciate the shapes and relations of objects with respect to one another (i.e., space-form blindness). As they grow older, affected children typically are shorter than normal. Although they do not develop breasts at puberty, some pubic or axillary hair may develop because appropriate adrenarche can occur with failure of thelarche (i.e., breast development). **Although less severe short stature and some adolescent development may occur with chromosomal mosaicism, it is reasonable to assume that any short, slowly growing, sexually infantile girl has Turner syndrome until proved otherwise because this disorder is so prevalent (about 1 in 2,500 newborn phenotypic females).** In fact, the 45,X karyotype is the single most frequent chromosomal disorder in humans, but most affected fetuses are aborted spontaneously early in pregnancy. However, trisomy is the most common chromosomal type or category of abnormality in first-trimester losses.



Figure 26.10 Typical appearance of two individuals with 45,X gonadal dysgenesis. **A:** This 16-year-old individual has obvious short stature, a webbed neck, shortened fourth metatarsals, and a thoracotomy scar from the repair of the coarctation of the aorta that was performed at 13 years of age. **B:** This 11-year-old individual also has obvious short stature and stigmata of Turner syndrome. Note that these two individuals look more like each other than they might look like any genetic siblings.

The short stature commonly associated with the Turner phenotype appears largely to be due to the loss of a homeobox-containing gene (which encodes for an osteogenic gene)

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located on the pseudoautosomal region (PAR 1) of the short arms of the X (Xp22) and Y (Yp11.3) chromosomes (32). This gene, which is called either *SHOX* (short stature homeobox-containing gene) or *PHOG* (pseudoautosomal homeobox osteogenic gene), escapes X inactivation because of its pseudoautosomal location. The gene appears to account for about two thirds of the height deficit commonly associated with Turner syndrome.

Even in the presence of typical Turner stigmata, a karyotype is indicated to eliminate the possibility of the presence of any portion of a Y chromosome. If a Y chromosome is identified, surgical extirpation of the gonads is warranted to eliminate any possibility of a germ

cell neoplasm (estimated 20%–30% prevalence) (33,34). In individuals in whom there is no evidence of neoplastic dissemination, the uterus may be left *in situ* for donor *in vitro* fertilization and embryo transfer. **Individuals with Turner syndrome are at increased risk of sudden death from aortic rupture or dissection resulting from cystic medial necrosis during pregnancy, and the risk may be as great as 2% or more** (35). Echocardiography and counseling about this risk is warranted before pregnancy is contemplated. The evaluation of other commonly involved organ systems should include a careful physical examination, with special attention to the cardiovascular system, and thyroid function tests (including antibody assessment), fasting blood glucose, renal function tests, and intravenous pyelography or a renal ultrasonography.

Treatment of Turner Syndrome

To increase final adult height, commonly accepted treatment strategies include use of *exogenous GH* (36,37,38). With recombinant human GH use, the average height gain has varied from 4 to 16 cm. It appears that early initiation of therapy (between 2–8 years of age), gradually increasing the dose, and continuing treatment for a mean of 7 years can lead to achievement of a final height greater than 150 cm in most patients (37). Weekly doses of *GH* of 0.375 mg/kg divided into seven daily doses are typical. It is not clear if an anabolic steroid such as *oxandrolone* will provide additional growth.

The gonadal steroid treatment of patients with Turner syndrome is as follows:

- **To promote sexual maturation, therapy with *exogenous estrogen* should be initiated when the patient is psychologically ready, at about 12 to 13 years of age, and after *GH* therapy has been administered for several years. Low-dose *estrogen* can be introduced at this time without compromising final adult height (39).**
- **Because the intent is to mimic normal pubertal development, therapy with low-dose *estrogen* alone (such as 0.025 mg/day *transdermal estradiol* or 0.3–0.625 mg *conjugated estrogens* orally each day) should be initiated.**
- **Progestins (5–10 mg *medroxyprogesterone acetate* or 200 mg *micronized progesterone* orally for 12–14 days every 1–2 months) can be added to prevent endometrial hyperplasia after the patient first experiences vaginal bleeding or after 6 months of unopposed *estrogen* use if the patient has not yet had any bleeding.**
- **The dose of *estrogen* is increased slowly over 1 to 2 years until the patient is taking about twice as much *estrogen* as the amount administered to postmenopausal women.**
- **Girls with gonadal dysgenesis must be monitored carefully for the development of hypertension with *estrogen* therapy.**
- **The patients and their parents should be counseled regarding the emotional and physical changes that will occur with therapy.**

Mosaic Forms of Gonadal Dysgenesis

Individuals with rare mosaic forms of gonadal dysgenesis may develop normally at puberty. The decision to initiate therapy with exogenous estrogen should be based mainly on circulating FSH levels. Levels in the normal range for the patient's age imply the presence of functional gonads.

These individuals can become pregnant, with success rates of more than 50% using donor oocytes (40). The increased risk of sudden death during pregnancy resulting from aortic rupture should be assumed to be similar to that of other women with the Turner phenotype (35).

Pure Gonadal Dysgenesis

The term *pure gonadal dysgenesis* refers to **46,XX or 46,XY phenotypic females who have streak gonads. This condition may occur sporadically or may be inherited as an autosomal recessive trait or as an X-linked trait in XY gonadal dysgenesis** (Fig. 26.11). Affected girls typically are of average height and have none of the stigmata of Turner syndrome, but they have elevated levels of FSH because the streak gonads produce neither steroid hormones nor inhibin. When gonadal dysgenesis occurs in 46,XY individuals, it is sometimes termed *Swyer syndrome*. Surgical extirpation is warranted in individuals with a 46,XY karyotype to prevent development of germ cell neoplasms. Both 46,XX and 46,XY forms of gonadal dysgenesis benefit from exogenous estrogen and are potential candidates for donor oocytes.

In early gonadal failure, the ovaries apparently develop normally but contain no oocytes by the expected age of puberty. These disorders are considered further in the discussion delineating the evaluation of amenorrhea (see Chapter 27).

Hypogonadotropic Hypogonadism

Hypothalamic-pituitary disturbances are usually associated with low levels of circulating gonadotropins (with both LH and FSH levels less than or equal to 10 mIU/mL) (41). There are both sporadic and familial causes of hypogonadotropic hypogonadism, and the differential diagnosis is extensive. **Mutations in several genes have been shown to cause hypogonadotropic hypogonadism in humans** (42). This condition can arise from abnormalities in hypothalamic GnRH secretion, impaired release of gonadotropins from the pituitary gland, or both. At least six separate genes have been identified as causes of hypogonadotropic hypogonadism: (i) *KAL1*, (ii) *FGFR1/KAL2*, (iii) *DAX 1* (the gene for X-linked congenital adrenal hypoplasia), (iv) *GNRHR* (the gene for the GnRH receptor), (v) *PC1* (the gene for prohormone convertase 1), and (vi) *GPR54* (encoding a G-protein coupled receptor) (43,44,45). Because defects in these genes account for less than 20% of all cases of isolated hypogonadotropic hypogonadism, additional mutations probably exist but have yet to be identified. It is important to remember, however, that low levels of LH and FSH are normally present in the prepubertal years; thus, girls with constitutionally delayed puberty may mistakenly be presumed to have hypogonadotropic hypogonadism. In fact, **constitutional delay is the most common cause of delayed puberty.** In a normal population, 2% to 3% of normal children will be classified as having pubertal delay, and this finding may be considered a normal variant. **Constitutional delayed growth and adolescence can be diagnosed only after careful evaluation excludes other causes of delayed puberty and normal sexual development is documented by longitudinal follow-up.** The farther below the third percentile for height that the young girl is, the less likely it is that the cause is constitutional. Because some children are severely handicapped socially by constitutional pubertal delay, some physicians occasionally provide *exogenous estrogen* in

low doses for 3 to 4 months to stimulate some pubertal development. However, the benefits of treatment are not well documented, and there is little evidence to support the idea that treatment improves psychosocial function.

Kallmann Syndrome

As originally described in 1944 (46), *Kallmann syndrome* **consisted of the triad of anosmia, hypogonadism, and color blindness in men. Women may be affected as well, and other associated defects may include cleft lip and palate,**

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cerebellar ataxia, nerve deafness, and abnormalities of thirst and vasopressin release.

The frequency approximates 1 in 10,000 men and 1 in 50,000 women. Because autopsy studies have shown partial or complete agenesis of the olfactory bulb, the term *olfactogenital dysplasia* has also been used to describe the disorder. These anatomic findings coincide with embryologic studies documenting that GnRH neurons originally develop in the epithelium of the olfactory placode and normally migrate into the hypothalamus (47). In some affected individuals, gene defects have been found in one protein, anosmin, that facilitates this neuronal migration, thus leading to an absence of GnRH neurons in the hypothalamus and olfactory bulbs and consequent hypogonadotropic hypogonadism and anosmia (Kallmann syndrome) (48). The gene defect resulting in loss of this facilitory

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adhesion protein has been localized to the Xp22.3 locus in an X-linked form of the syndrome, and this locus has been designated *KAL 1*. Because confirmed mutations in the coding sequence of the *KAL* gene occur only in a minority of individuals with Kallmann syndrome (49), other mutations no doubt will be identified in the future. Moreover, the disorder is so heterogeneous that it appears likely that it forms a structural continuum with other midline defects. Septo-optic dysplasia represents the most severe form of the disorder.

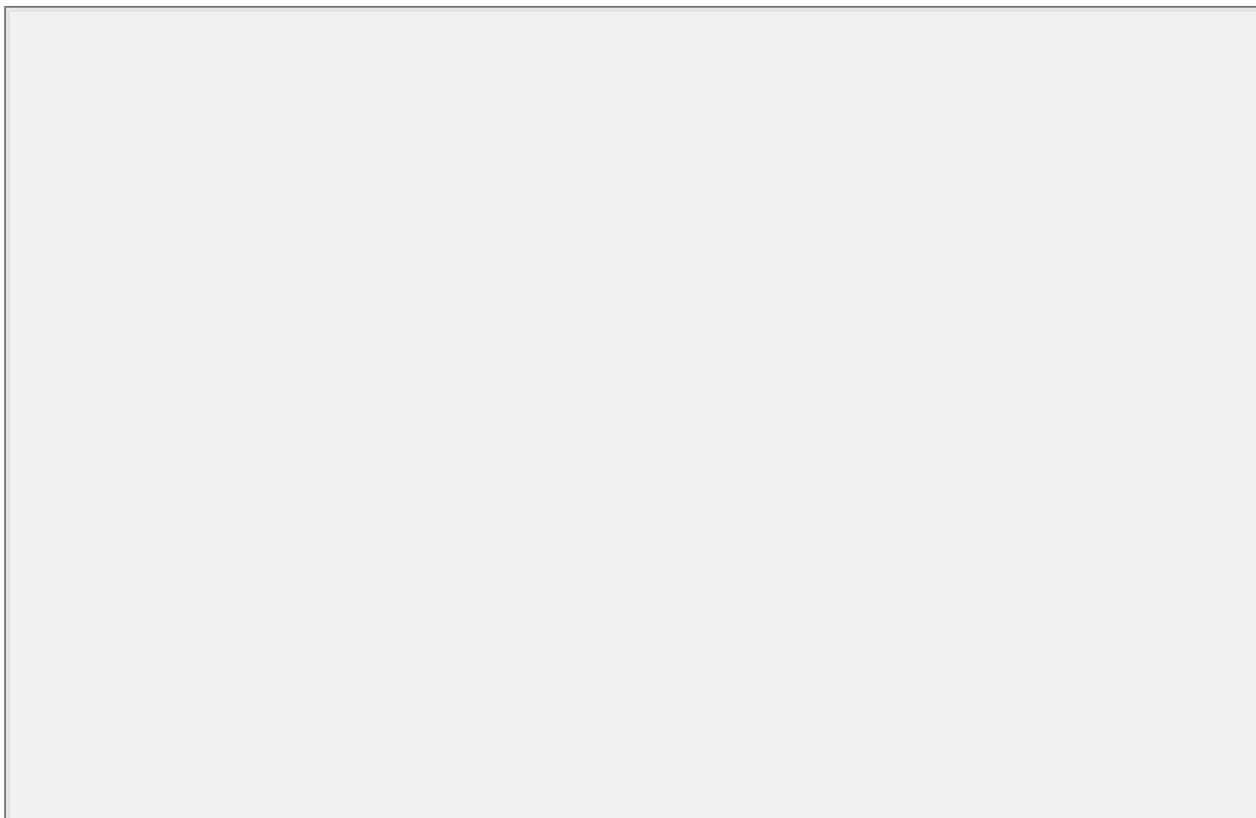




Figure 26.11 A: A 16-year-old individual with 46,XX gonadal dysgenesis and primary amenorrhea. Circulating follicle-stimulating hormone (FSH) levels were markedly elevated. The small amount of breast development (Tanner stage 2) is unusual, but some pubertal development may occur in such patients. **B:** A 16-year-old individual with 46,XY gonadal dysgenesis who presented with primary amenorrhea and markedly elevated FSH levels. Most affected individuals do not present with as much pubic and axillary hair development. The right gonad contained a dysgerminoma, but there was no evidence of metastases. (From **Rebar RW**. Normal and abnormal sexual differentiation and pubertal development. In: **Moore TR, Reiter RC, Rebar RW, et al**, eds. *Gynecology and obstetrics: a longitudinal approach*. New York, NY: Churchill Livingstone, 1993:97-133, with permission.) **C:** Clitoromegaly noted in the girl with 46,XY gonadal dysgenesis depicted in Figure 26.11B. **D:** The same individual as depicted in Figure 26.11B and D with 46,XY gonadal dysgenesis 1 year after gonadectomy and replacement with exogenous estrogen.

Clinically, affected individuals typically present with sexual infantilism and an eunuchoid habitus, but some degree of breast development may occur (Fig. 26.12).

Primary amenorrhea is the rule. The ovaries are usually small, with follicles seldom developing beyond the primordial stage. Circulating gonadotropin levels are usually very low but almost invariably measurable. Affected individuals respond readily to pulsatile administration of exogenous GnRH, and clearly this is the most physiologic approach to ovulation induction (40). For women not seeking pregnancy, therapy with exogenous estrogen and progestin is indicated.

Isolated gonadotropin deficiency can also occur in association with the Prader-Labhart-Willi syndrome, which is characterized by obesity, short stature, hypogonadism, small hands and feet (acromicria), mental retardation, and infantile hypotonia. When the syndrome occurs in association with the Laurence-Moon-Bardet-Biedl syndrome, retinitis pigmentosa, postaxial polydactyly, obesity, and hypogonadism also may be present. Prader-Labhart-Willi syndrome apparently results from rearrangements of chromosome 15q11 to q13, an imprinted region of the human genome (50). Laurence-Moon-Bardet-Biedl syndrome, inherited in an autosomal recessive manner, is apparently heterogeneous, with at least four involved gene loci having been mapped to date (51).

Multiple pituitary hormone deficiencies, which are usually hypothalamic in origin, may be congenital and either part of an inherited constellation of findings or sporadic. If GH or thyroid-stimulating hormone (TSH) concentrations are subnormal, growth and pubertal development will be affected. Thus, the condition should be diagnosed before the age of puberty. Because individuals with hypopituitarism have a high mortality rate, predominantly caused by vascular and respiratory disease (52), it is important to identify affected individuals. Later age at diagnosis, female sex, and above all craniopharyngioma have been identified as significant independent risk factors. Untreated gonadotropin deficiency also is an important risk factor for early mortality.

Tumors of the Hypothalamus and Pituitary

Several different tumors of the hypothalamic and pituitary regions also may lead to hypogonadotropic hypogonadism (53) (Fig. 26.13A). Except for craniopharyngiomas, these tumors are relatively uncommon in children. Craniopharyngiomas are usually suprasellar in location and may be asymptomatic well into the second decade of life. Such tumors may present as headache, visual disturbances, short stature or growth failure, delayed puberty, or diabetes insipidus. Visual field defects (including bilateral temporal hemianopsia), optic atrophy, or papilledema may be seen on physical examination. Laboratory evaluation should

document hypogonadotropism and may also reveal hyperprolactinemia as a result of interruption of hypothalamic dopamine inhibition of prolactin release. Radiographically, the tumor may be either cystic or solid and may show areas of calcification. Appropriate therapy for hypothalamic–pituitary tumors may involve surgical excision or radiotherapy (with adequate pituitary hormone replacement therapy) and is best managed by a team of physicians that includes an endocrinologist, a neurosurgeon, and a radiotherapist.

Other Central Nervous System Disorders

Other central nervous system disorders that may lead to delayed puberty include infiltrative diseases, such as Langerhans cell–type

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histiocytosis, particularly the form known previously as *Hand–Schüller-Christian disease* (Figs. 26.13B and 26.13C). Diabetes insipidus is the most common endocrinopathy (because of infiltration of the supraoptic nucleus in the hypothalamus), but short stature resulting from GH deficiency and delayed puberty caused by gonadotropin deficiency are not uncommon in this disorder (54).





Figure 26.12 Left A 21½-year-old woman with Kallmann syndrome. Note that the patient has some pubic and axillary hair. Bone age was 16 years. It is rare to see affected individuals today who were not given oral contraceptive agents to induce menses (with some consequent breast development). (From **Wilkins L.** *The diagnosis and treatment of endocrine disorders in childhood and adolescence.* 3rd ed. Springfield, IL: Charles C Thomas, 1965, with permission.).





Figure 26.13 Right A: A 16-year-old girl with delayed puberty. Breast budding began at 11 years of age, but there was no further development. During the year before presentation, her scholastic performance in school deteriorated, she gained 25 lb, she became increasingly lethargic, and nocturia and polydipsia were noted. Initial evaluation documented low follicle-stimulating hormone, elevated prolactin, and a bone age of 10.5 years. Computed tomography scanning documented a large hypothalamic neoplasm that proved to be an ectopic germinoma. The patient was also documented to be hypothyroid and hypoadrenal and to have diabetes insipidus. Despite the elevated prolactin, she had no galactorrhea because of the minimal breast development. (From **Rebar RW**. Normal and abnormal sexual differentiation and pubertal development. In: **Moore TR, Reiter RC, Rebar RW, et al**, eds. *Gynecology and obstetrics: a longitudinal approach*. New York, NY: Churchill Livingstone, 1993:97-133, with permission.). B: A 16-year-old girl (frontal view) with primary amenorrhea who progressed in puberty until about 12 years of age. Breast budding occurred at about 10 years of age. The patient's short stature is obvious. She proved to have hypopituitarism. Classic radiographic findings established the diagnosis of Langerhans cell-type histiocytosis (Hand-Schüller-Christian disease). C: Side view of girl shown in Figure 26.13B.

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Irradiation of the central nervous system for treatment of any neoplasm or leukemia may result in hypothalamic dysfunction. Although GH deficiency is the most frequent finding, partial or complete gonadotropin deficiency may develop in some patients.

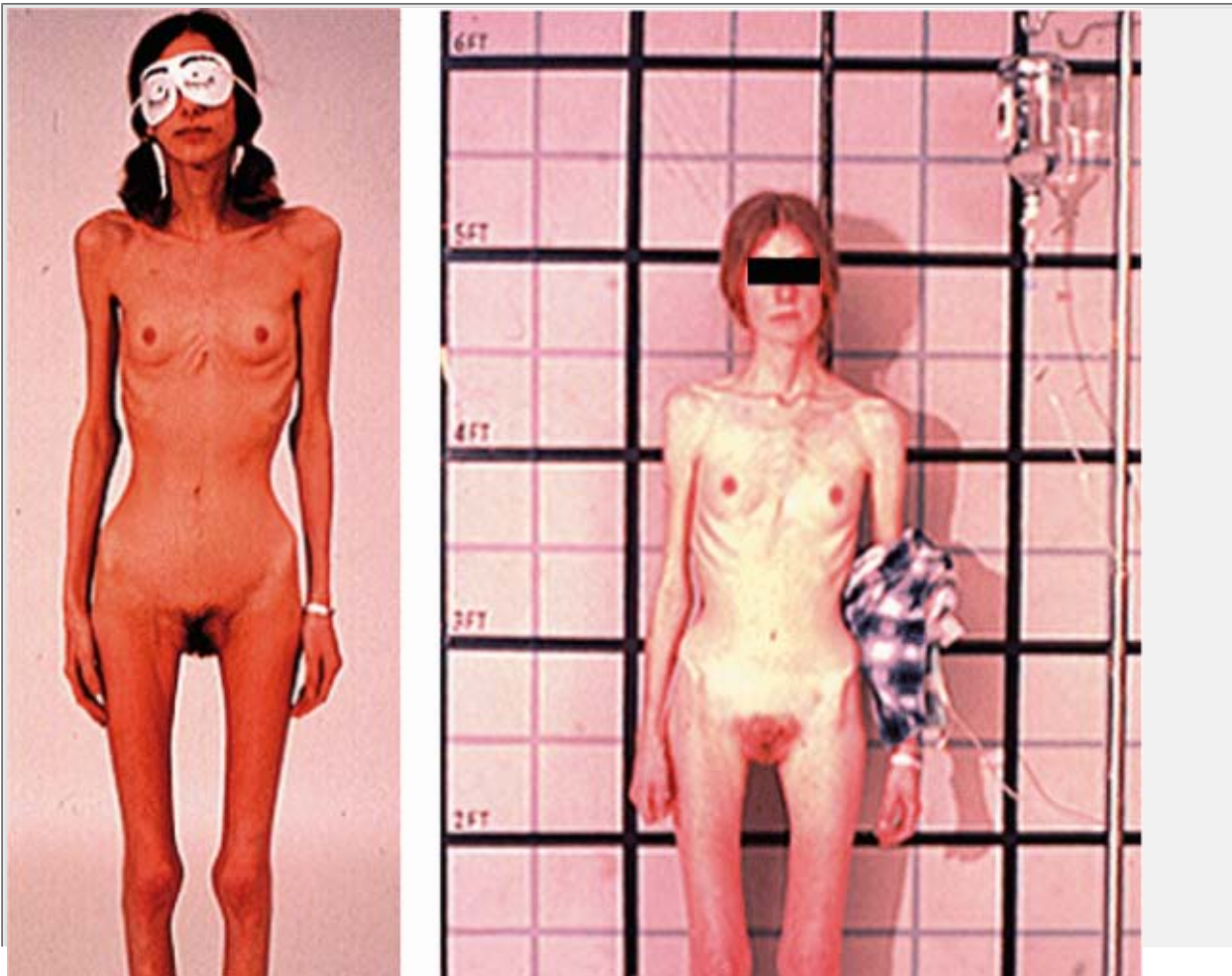
Severe chronic illnesses, often accompanied by malnutrition, also may lead to slowed growth in childhood and delayed adolescence. Regardless of the cause, weight loss to less than 80% to 85% of ideal body weight often results in hypothalamic GnRH deficiency. If adequate body weight and nutrition are maintained in chronic illnesses such as Crohn disease or chronic pulmonary or renal disease, sufficient gonadotropin secretion usually is present to initiate and maintain pubertal development.

Anorexia Nervosa and Bulimia

Significant weight loss and psychological dysfunction occur simultaneously with anorexia nervosa (55,56). Although many anorectic girls experience amenorrhea after pubertal development has begun, if the disorder begins sufficiently early, pubertal development may be delayed or interrupted (Fig. 26.14). **The following constellation of associated findings confirms anorexia nervosa in most individuals:**

- **Relentless pursuit of thinness.**
 - **Amenorrhea, sometimes preceding the weight loss.**
 - **Extreme inanition.**
 - **Obsessive–compulsive personality often characterized by overachievement.**
-
- **Distorted and bizarre attitude toward eating, food, or weight.**
 - **Distorted body image.**

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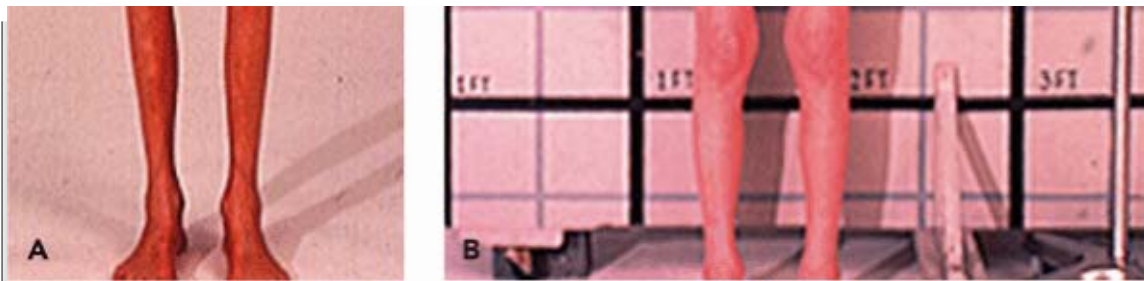


Figure 26.14 A: A 20-year-old college woman with anorexia nervosa. B: A 16-year-old student with anorexia nervosa. In both cases, as is true of most such patients, pubertal development had been completed and menses initiated before anorexia led to marked weight loss.

Because normal body weight is commonly maintained in bulimia, it is unusual for bulimic patients to experience either delayed development or amenorrhea. Girls with anorexia nervosa may have, in addition to hypogonadotropic hypogonadism, partial diabetes insipidus, abnormal temperature regulation, chemical hypothyroidism with low serum triiodothyronine (T_3) and high reverse T_3 levels, and elevated circulating cortisol levels in the absence of evidence of hypercortisolism (57).

Fear of obesity, a syndrome of self-induced malnutrition common among teenage gymnasts and ballet dancers, also may slow growth and delay pubertal development (58). These children voluntarily reduce their caloric intake as much as 40%, leading to nutritional growth retardation. An additive role for endurance training in the delayed development is possible, but the mechanisms are unclear at this point. These conditions are essentially severe forms of hypothalamic amenorrhea. It is clear, however, that delayed puberty will occur inevitably unless adequate caloric intake is provided.

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Hyperprolactinemia

Low levels of LH and FSH may be associated with hyperprolactinemia. As noted, galactorrhea cannot occur in the absence of complete breast development. Pituitary prolactinomas are rare during adolescence but must be considered when certain signs and symptoms are present. **Many individuals with prolactinomas have a history of delayed menarche.** The association between the ingestion of certain drugs (most often psychotropic agents and opiates in this age group) is well established. Primary hypothyroidism also is associated with hyperprolactinemia because increased levels of thyrotropin-releasing hormone (TRH) stimulate secretion of prolactin. The *empty sella syndrome*, in which the sella turcica is enlarged but has been replaced by cerebrospinal fluid, may also be associated with hyperprolactinemia.

Use of Chemotherapeutic Agents

As survival rates following treatment for childhood malignancy improve, the effects of cancer therapy become ever more important. **Both radiation therapy to the abdomen and systemic chemotherapeutic agents, particularly alkylating agents, have toxic effects on germ cells. Although prepubertal gonads appear less vulnerable than those of adults, ovarian failure is common.** An argument can be made for endocrine assessment as early as 1 year following completion of therapy to identify children who will suffer from hypogonadism. Spontaneous ovarian activity can resume even years after therapy.

Asynchronous Puberty

Asynchronous pubertal development is characteristic of androgen insensitivity (i.e., testicular feminization). **Affected individuals typically present with breast development (usually only to Tanner stage 3) out of proportion with the amount of pubic and axillary hair present (Fig. 26.15).** In this disorder, 46,XY individuals have bilateral testes, female external genitalia, a blindly ending vagina (often foreshortened and sometimes absent), and no müllerian derivatives (i.e., uterus and fallopian tubes) (59). Infrequently, patients may have clitoral enlargement and labioscrotal fusion at puberty, which is referred to as *incomplete androgen insensitivity*.

Asynchronous puberty is heterogeneous but is always related to some abnormality of the androgen receptor or of androgen action (60). In perhaps 60% to 70% of cases, androgen receptors cannot be detected (i.e., the patient is receptor negative). In the remaining cases, androgen receptors are present (i.e., receptor positive), but mutations in the androgen receptor have been detected or there is a defect at a more distal step in androgen action (i.e., a postreceptor defect). Receptor-positive individuals are indistinguishable clinically from receptor-negative individuals. Several different mutations in the androgen receptor gene, most of which occur within the androgen-binding domain of the receptor, have been identified in affected individuals who are receptor positive. Severe X-linked androgen receptor gene mutations cause complete androgen insensitivity, whereas mild mutations impair virilization with or without infertility, and moderate mutations result in a wide phenotypic spectrum of expression among siblings (61).

Because the Sertoli cells of the testes make antimüllerian hormone (AMH), müllerian derivatives are absent in this disorder; thus, müllerian regression occurs normally. The testes are often normal in size and may be located anywhere along the path of embryonic testicular descent—in the abdomen, inguinal canal, or labia. Half of all individuals with androgen insensitivity develop inguinal hernias. Recognizing that most such girls will be 46,XX, it is important to determine the karyotype in prepubertal girls with inguinal hernias, especially if a uterus cannot be detected with certainty by ultrasound.

The frequency of gonadal neoplasia is increased with this condition, but the extent is uncertain (33). Most clinicians believe the risk for neoplasia is low before 25 years of age;

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thus, **the testes should be left in place until after pubertal feminization, especially because the risk of neoplasia appears to increase with age.** Exogenous estrogen should be provided after gonadectomy.

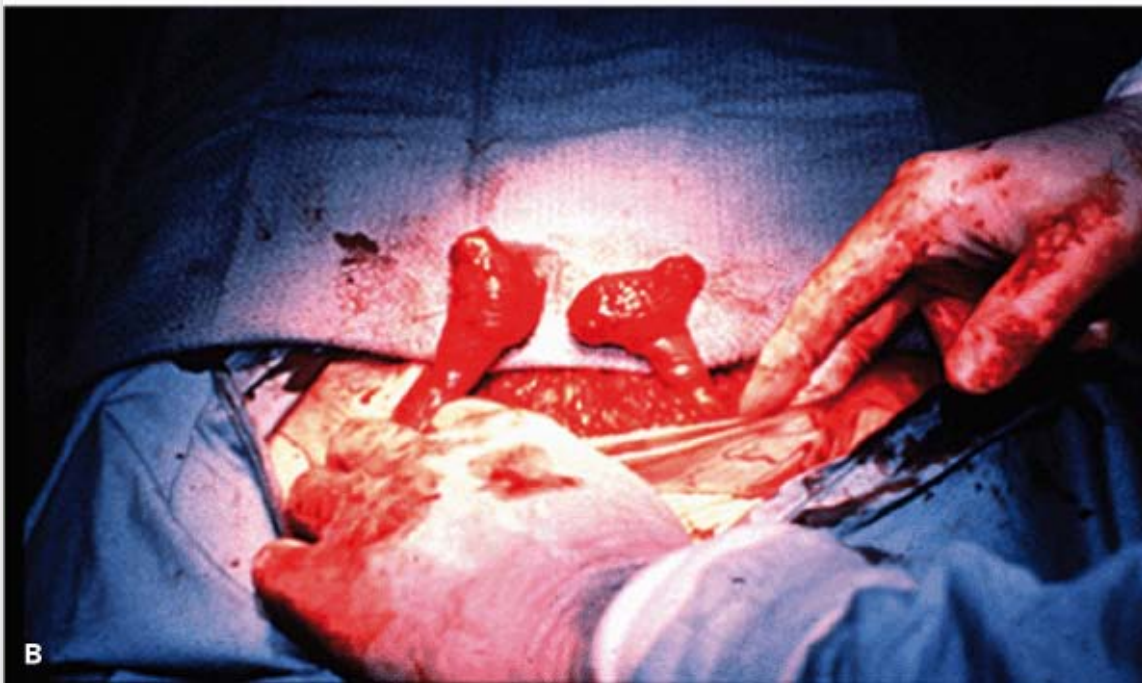


Figure 26.15 A: This 17-year-old individual presented with primary amenorrhea and was found to have a blind-ending vagina and bilateral inguinal masses. Circulating levels of testosterone were at the upper limits of the normal range for men, and the karyotype was 46,XY, confirming androgen insensitivity. **B:** Two inguinal testes were found at surgery. (From **Simpson JL, Rebar RW.** Normal and abnormal sexual differentiation and development. In: **Becker KL,** ed. *Principles and practice of endocrinology and metabolism*. 2nd ed. Philadelphia, PA: JB Lippincott, 1995: 788–822, with permission.)

The diagnosis is often suspected by the typical physical findings and strongly suggested by normal (or even somewhat elevated) male levels of testosterone, normal or somewhat elevated levels of LH, and normal levels of FSH. The diagnosis is confirmed by a 46,XY karyotype.

Interacting with the patient and family requires sensitivity and care. It may be inadvisable to begin by informing the patient of the karyotype; the psychological implications may be devastating because the patient has been reared as a girl. Family members should be informed initially that müllerian aplasia occurred and that the risk for neoplasia mandates gonadectomy after puberty. Because the disorder can be inherited in an X-linked recessive fashion, families should undergo appropriate genetic counseling and screening to identify the possible existence of other affected family members.

Precocious Puberty

Although precocious pubertal development may be classified in several ways, it is perhaps simplest to think of the development as gonadotropin dependent (in which case it is almost invariably of central origin) or gonadotropin independent (of peripheral origin). Precocious puberty is 20 times more common in girls than in boys. In fully 90% of girls, the precocious development is idiopathic, whereas this appears to be true for only 10% of boys. Family history, the rapidity with which secondary sexual characteristics are developing, the rate of growth, and the presence or absence of central nervous system disease should all be considered in deciding whether to pursue evaluation of a girl for precocious puberty. The evaluation of precocious puberty is as follows: .

- **Measurement of basal gonadotropin levels is the first step in the evaluation of a child with sexual precocity** (Fig. 26.16).
- **Thyroid function should also be evaluated** to rule out primary hypothyroidism as the cause of precocious development.
- **High levels of LH (which really may be human chorionic gonadotropin detected because of cross-reactivity with LH in immunoassays) suggest a gonadotropin-producing neoplasm**, most often a pinealoma (ectopic germinoma) or choriocarcinoma or, less often, a hepatoblastoma. (Gonadotropin-producing neoplasms are the only causes of precocious puberty in which the gonadotropin dependence does not equate with central precocious puberty.)
- **Low or pubertal levels of gonadotropins indicate the need to determine circulating estradiol concentrations in girls with isosexual development** and to assess androgen levels, specifically testosterone, DHEAS, and 17 α -hydroxyprogesterone in girls

with heterosexual development.

- **Increased estradiol levels suggest an estrogen-secreting neoplasm, probably of ovarian origin.**

- **Increased testosterone levels suggest an androgen-producing neoplasm of the ovary or the adrenal gland.** Such neoplasms may be palpable on abdominal or rectal examination. Increased 17 α -hydroxyprogesterone levels are diagnostic

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of 21-hydroxylase deficiency (ie, congenital adrenal hyperplasia [CAH]). Levels of DHEAS are elevated in various forms of CAH as well.

- **If the estradiol levels are compatible with the degree of pubertal development observed, evaluation of the central nervous system by MRI or CT scanning is warranted.**

- **Bone age should always be assessed in evaluating an individual with sexual precocity.**

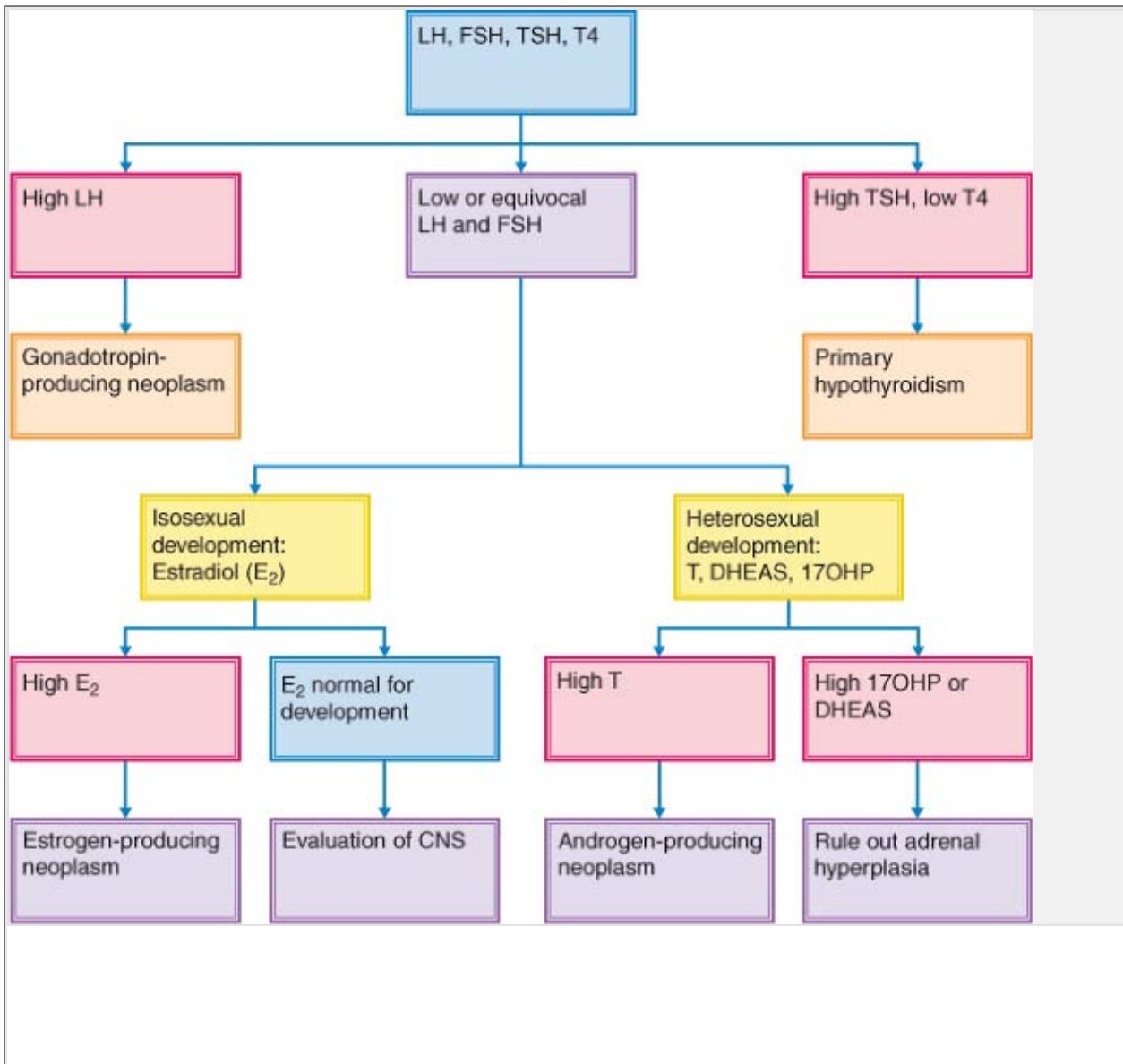


Figure 26.16 Flow diagram for the evaluation of precocious puberty in phenotypic

females. LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; T, testosterone; DHEAS, dehydroepiandrosterone sulfate; 17OHP, 17-hydroxyprogesterone; CNS, central nervous system. (From **Rebar RW**. Normal and abnormal sexual differentiation and pubertal development. In: **Moore TR, Reiter RC, Rebar RW, et al.**, eds. *Gynecology and obstetrics: a longitudinal approach*. New York, NY: Churchill Livingstone, 1993:97–133, with permission.)

Perhaps the most difficult decision for the gynecologist is determining how much evaluation is warranted for the young girl brought in by her mother for precocious breast budding only (*precocious thelarche*) or the appearance of pubic or axillary hair alone (*precocious pubarche* or *adrenarche*) (Fig. 26.17). In such cases, it is acceptable to many clinicians to follow the patient at frequent intervals and to proceed with evaluation if there is evidence of pubertal progression. The feasibility of this approach may depend on the concerns of the parents. Premature thelarche may be caused by

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increased sensitivity of the breasts to low levels of estrogen or to increased estradiol secretion by follicular cysts. Premature adrenarche or pubarche may be due to increased sensitivity to low levels of androgens and must be distinguished from late-onset (nonclassic) CAH. If there is no evidence of breast development and the appearance of sexually stimulated hair (i.e., precocious puberty) or of progression, these conditions are virtually always benign.

Some girls with premature adrenarche are at risk of developing polycystic ovarian syndrome (PCOS) (62). Although mean androgen levels are within the normal range, a significant minority have an exaggerated response to corticotropin stimulation. Moreover, the magnitude of this response is inversely related to insulin sensitivity. Thus, premature adrenarche may be the first sign of insulin resistance or PCOS in some individuals. Treatment of coexisting obesity and long-term follow-up are indicated to address potential complications of PCOS and insulin resistance.

Constitutional (idiopathic) sexual precocity is the most common cause of precocious puberty. It is often familial and represents the so-called "tail" of the gaussian curve (i.e., the early 2.5% for the age distribution for the onset of puberty). In many of these girls, puberty is slowly progressive, but in a few, development progresses rapidly. The major complication of sexual precocity is limitation of height. Thus, therapy, may be warranted to prevent this consequence.

Central (True) Precocious Puberty

In central precocious puberty, GnRH prematurely stimulates increased gonadotropin secretion. Central precocious puberty may occur in children in whom there is no structural abnormality, in which case it is termed *constitutional* or *idiopathic*.

Alternatively, central precocious puberty may result from a tumor, infection, congenital abnormality, or traumatic injury affecting the hypothalamus. Tumors of the hypothalamus include hamartomas and, less frequently, neurogliomas and pinealomas. It appears that hamartomas produce GnRH in a pulsatile manner and thus stimulate gonadotropin secretion (63) (Fig. 26.18). A number of congenital malformations, including hydrocephalus, craniostenosis, arachnoid cysts, and septo-optic dysplasia, also can be associated with precocious puberty (as well as with sexual infantilism).

Precocious Puberty of Peripheral Origin

In gonadotropin-independent precocious puberty, production of estrogens or androgens from the ovaries, adrenals, or rare steroid-secreting neoplasms leads to early pubertal development. Small functional ovarian cysts, typically asymptomatic, are common in children and may cause transient sexual precocity (64). Simple cysts (with a benign ultrasonographic appearance) can be observed and usually resolve over time. Of the various ovarian neoplasms that can secrete estrogens, granulosa-theca cell tumors occur most frequently but are still rare (65). Although such tumors may grow rapidly, more than two thirds are benign.

The *McCune-Albright syndrome* is characterized by **polyostotic fibrous dysplasia of bone, irregular café-au-lait spots on the skin**, and hyperfunctioning endocrinopathies. Girls develop sexual precocity as a result of functioning ovarian cysts. Other endocrinopathies may include hyperthyroidism, hypercortisolism, hyperprolactinemia, and acromegaly. It is now known that mutations of the G α subunit of the G protein, which couples extracellular hormonal signals to the activation of adenylate cyclase, are responsible for the autonomous hyperfunction of the endocrine glands and, presumably, for the other defects present in this disorder (66). Exposure to exogenous estrogens can mimic gonadotropin-independent precocious puberty. Ingestion of oral contraceptives, other estrogen-containing pharmaceutical agents, and estrogen-contaminated foods, as well as the topical use of estrogens, have been implicated in cases of precocious development in infants and children. Severe primary

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hypothyroidism has also been associated with sexual precocity; associated hyperprolactinemia may result in galactorrhea in affected individuals.

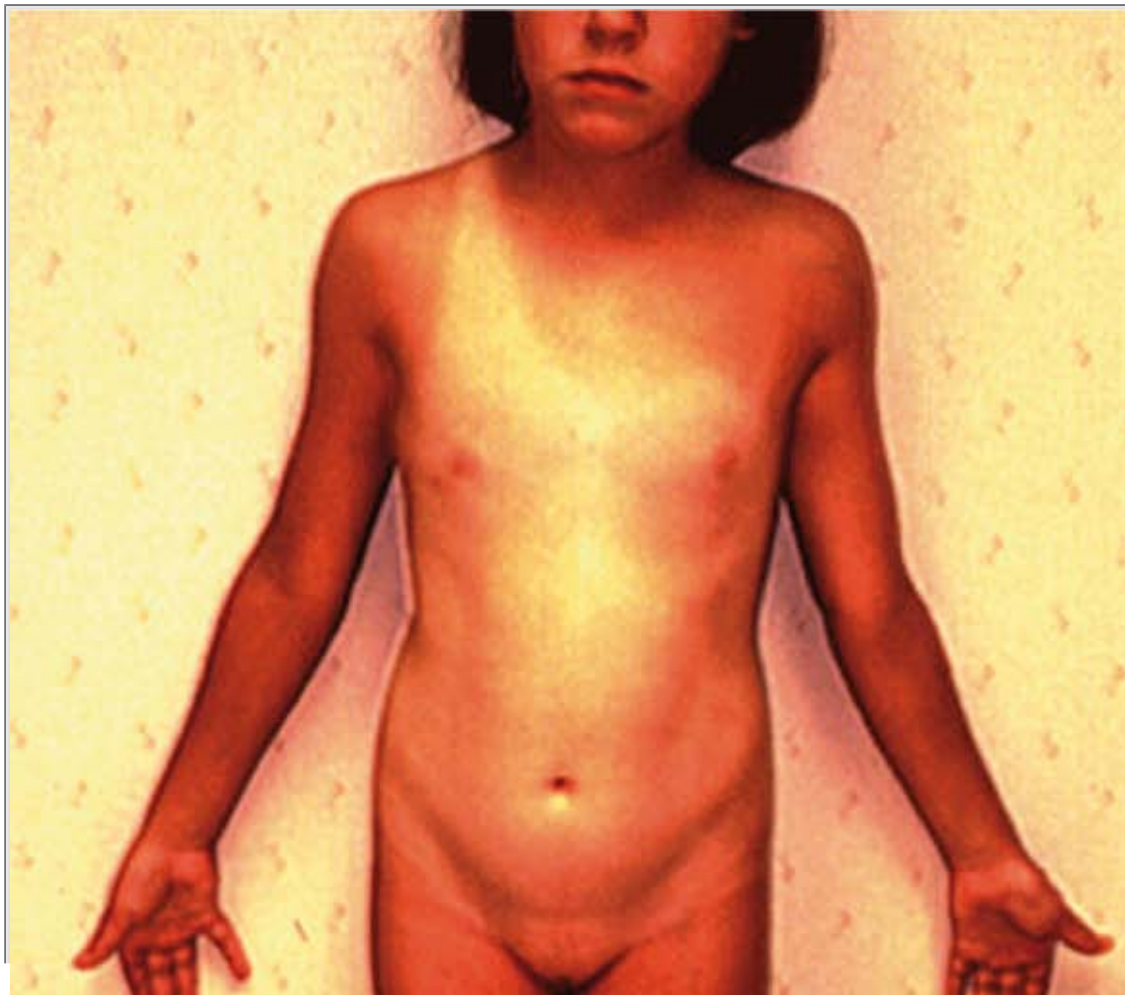




Figure 26.17 Five-year-old girl with development of pubic hair (A) as shown more closely in (B) (precocious adrenarche). Gonadotropin levels were prepubertal, and bone age was appropriate for age. No further development occurred until breast budding at approximately age 9.

Congenital Adrenal Hyperplasia

Heterosexual precocious puberty is always of peripheral origin and is most often caused by CAH. Three adrenal enzyme defects—21-hydroxylase deficiency, 11 β -hydroxylase deficiency, and 3 β -hydroxysteroid dehydrogenase deficiency—can lead not only to heterosexual precocity but also to virilization of the external genitalia because of increased androgen production beginning *in utero* (67). The clinical presentation of the various forms of CAH depends on the following factors: (i) the affected enzyme, (ii) the extent of residual enzymatic activity, and (iii) the physiologic consequences of deficiencies in the end products and excesses of precursor steroids.

21-Hydroxylase Deficiency

Most patients with classic CAH have 21-hydroxylase deficiency (Fig. 26.19). All forms of 21-hydroxylase deficiency are caused by homozygous or compound heterozygous mutations in the human *CYP21A2* gene, which encodes the 21-hydroxylase enzyme; in the carrier, heterozygote state, only one allele is mutated (68). Two *CYP21A2* genes, a 3' *CYP21A2B* gene encoding the functional enzyme and a pseudogene termed *CYP21A2A*, are situated very close to each other within the major histocompatibility locus on the short arm of chromosome 6. At least one fourth of cases of 21-hydroxylase deficiency are due to unequal crossover and

genetic recombination between the two genes during meiosis. However, severe mutations do not correlate with severe phenotype, and phenotypic variability likely depends on the activity of other interacting genes.

Neonatal screening suggests an incidence of about 1 in 15,000 births. Because of the location of the gene within the major histocompatibility locus, siblings with 21-hydroxylase deficiency usually have identical human leukocyte antigen (HLA) types. There are various forms of 21-hydroxylase deficiency, including simple virilizing or classic (typically identified at birth because of genital ambiguity), salt-wasting (in which there is impairment of mineralocorticoid as well as glucocorticoid secretion), and late-onset or nonclassic (in which heterosexual development occurs at the expected age of puberty). The nonclassic form is discussed in the following section on heterosexual pubertal development.

Deficiency of 21-hydroxylase results in the impairment of the conversion of 17 α -hydroxyprogesterone to 11-deoxycortisol and of progesterone to deoxycorticosterone (Fig. 26.20). As a consequence, precursors accumulate, and there is increased conversion to adrenal androgens. Because the development of the external genitalia is controlled by androgens, in the classic form of this disorder, girls are born with ambiguous genitalia, including an enlarged clitoris and fusion of the labioscrotal folds and the urogenital sinus. The internal female organs (including the uterus, fallopian tubes, and ovaries) develop normally because they are not affected by the increased androgen levels. Almost two thirds of affected newborns rapidly develop salt-wasting 21-hydroxylase deficiency, hyponatremia, hyperkalemia, and hypotension. During childhood, untreated girls with either the classic or salt-wasting form grow rapidly but have advanced bone ages, enter puberty early, experience early closure of their epiphyses, and ultimately are short in stature as adults. CAH, with appropriate therapy, is the only inherited disorder of sexual differentiation in which normal pregnancy and childbearing are possible. The classic and salt-wasting forms of 21-hydroxylase deficiency are easily diagnosed based on the presence of genital ambiguity and markedly elevated levels of 17 α -hydroxyprogesterone. Some states have initiated neonatal screening programs to detect 21-hydroxylase deficiency at birth.

3 β -Hydroxysteroid Dehydrogenase

Deficiency of 3 β -hydroxysteroid dehydrogenase (3 β -HSD), caused by mutations in the *HSD3B2* gene encoding the 3 β -HSDII enzyme,

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affects the synthesis of glucocorticoids, mineralocorticoids, and sex steroids. Typically, levels of 17-hydroxypregnenolone and DHEA are elevated (see Fig. 26.20). The classic form of the disorder, detectable at birth, is quite rare, and affected girls may be masculinized only slightly. In severe cases, salt wasting may also be present.

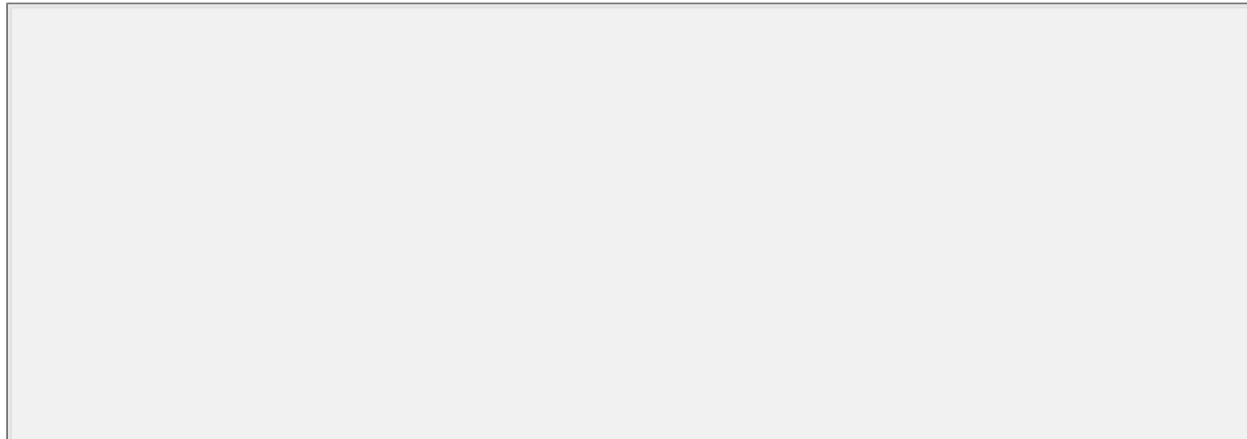




Figure 26.18 Left: A 7½-year-old girl with Tanner stage 4 pubertal development who began menstruating 1 month earlier. She was 57 inches tall (above the ninety-fifth percentile). Luteinizing hormone and follicle-stimulating hormone levels were consistent with her development. A large neoplasm that proved to be a hypothalamic hamartoma was present on computed tomography scan. Pubertal development began at about 5 years of age.



Figure 26.19 Right: A: A 10½-year-old girl with 21-hydroxylase deficiency before treatment. 17-Ketosteroid (KS) excretion was 34 mg/day. **B:** The same patient after 9 months of therapy with cortisone (17-KS excretion: 4.6 mg/day). (From **Wilkins L.** *The diagnosis and treatment of endocrine disorders in childhood and adolescence*. 3rd ed. Springfield, IL: Charles C Thomas, 1965: 439, with permission.).

A nonclassic form of this disorder may be associated with heterosexual precocious pubertal development (as is the classic form if untreated), but postpubertal hyperandrogenism occurs more often. The androgen excess in individuals with nonclassic 3β -HSD deficiency appears to result from androgens derived from the peripheral conversion of increased serum concentrations of DHEA. This disorder is inherited in autosomal recessive fashion, with allelism at the 3β -HSD gene on chromosome 1 believed to be responsible for the varying degrees of enzyme deficiency.

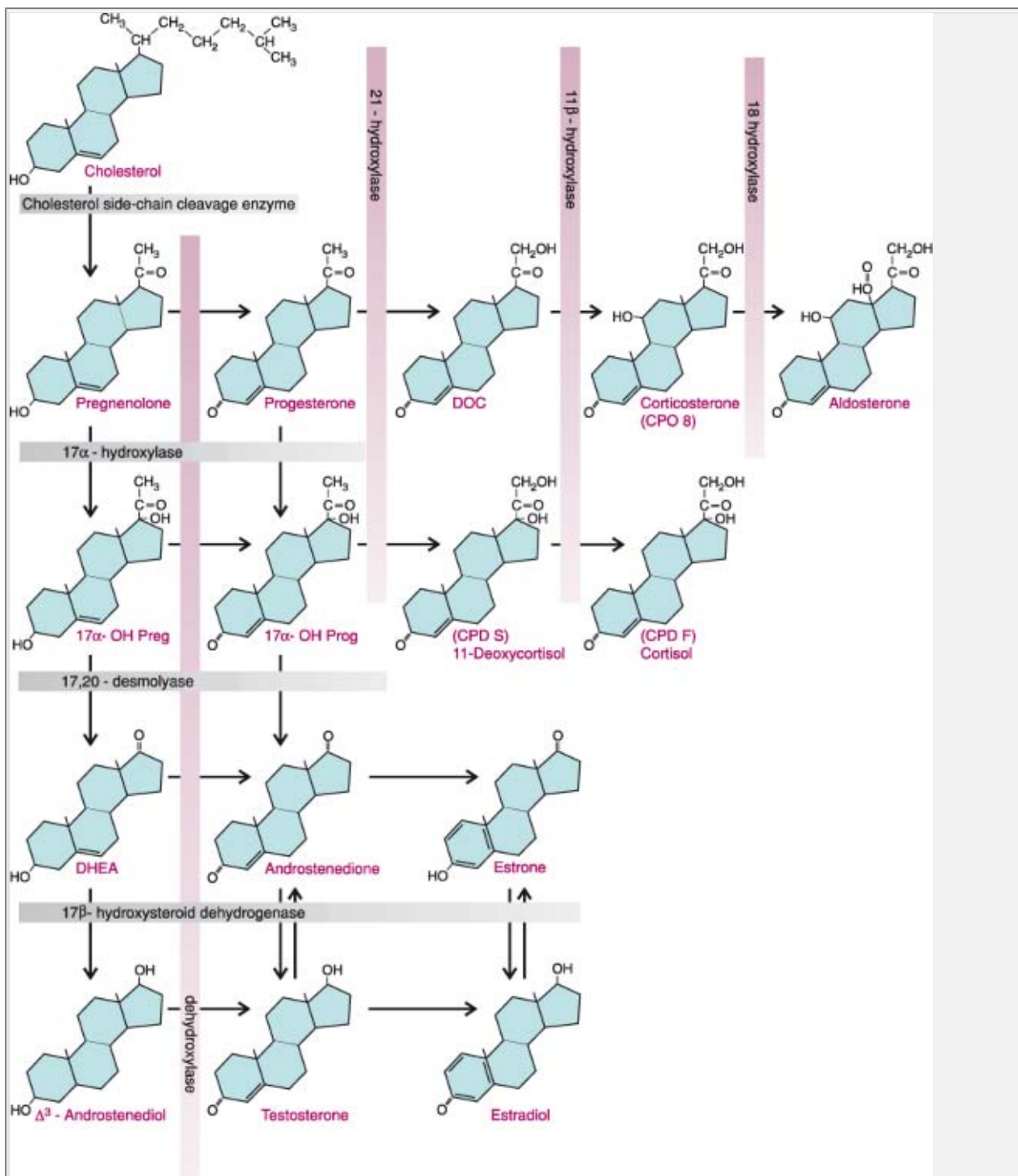


Figure 26.20 Gonadal and adrenal steroid pathways and the enzymes required for steroid conversion. DOC = deoxycorticosterone; 17 α -OH Preg = 17 α -hydroxypregnenolone; 17 α -OH Prog = 17 α -hydroxyprogesterone; DHEA = dehydroepiandrosterone sulfate. (From **Rebar RW, Kenigsberg D, Hodgen GD.** The normal menstrual cycle and the control of ovulation. In: **Becker KL,** ed. *Principles and practice of endocrinology and metabolism.* 2nd ed. Philadelphia, A: JB Lippincott, 1995:868–880, with permission.).

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11-Hydroxylase Deficiency

The classic form of 11-hydroxylase deficiency is believed to constitute 5% to 8% of all cases of CAH. Deficiency in 11-hydroxylase, caused by mutations in the *CYP11B1* gene, results in the inability to convert 11-deoxycortisol to cortisol and the consequent accumulation of androgen precursors (see Fig. 26.20). Markedly elevated levels of 11-deoxycortisol and deoxycorticosterone are present in the disorder. Because deoxycorticosterone acts as a mineralocorticoid, many individuals with this disorder become hypertensive. A mild nonclassic form of 11-hydroxylase deficiency has been reported but apparently is very uncommon.

Treatment of Congenital Adrenal Hyperplasia

The treatment of CAH involves providing replacement doses of the deficient steroid hormones. *Hydrocortisone* (10–20 mg/m² body surface area) or its equivalent is given daily in divided doses to suppress the elevated levels of pituitary corticotropin present and thus suppress the elevated androgen levels. With such treatment, signs of androgen excess should regress. In children, growth velocity and bone age should be monitored carefully because both overreplacement and underreplacement can result in premature closure of the epiphyses and short stature. Data now indicate that early diagnosis and compliance with therapy lead to adult height within 1 standard deviation of the anticipated target height in girls with 21-hydroxylase deficiency (69).

Mineralocorticoid replacement is generally required in individuals with 21-hydroxylase deficiency whether or not they are salt losing. The intent of glucocorticoid therapy should be to suppress morning 17 α -hydroxyprogesterone levels to between 300 and 900 ng/dL. Sufficient *fluorocortisone* should be given daily to suppress plasma renin activity to less than 5 mg/mL per hour.

Girls with ambiguous genitalia may require reconstructive surgery, including clitoral recession and vaginoplasty. Timing of such surgery is debated, but the girl must be of appropriate size to permit the surgery to be as simple as possible.

Heterosexual Pubertal Development

The most common cause of heterosexual development at the expected age of puberty is **PCOS (Fig. 26.21)**. **Because the syndrome is heterogeneous and poorly defined, clinical difficulties result in diagnosis and management (70).** **For the sake of simplicity,** PCOS may be defined as LH-dependent hyperandrogenism **(71)**. **Most clinical manifestations arise as a consequence of the hyperandrogenism and often include hirsutism beginning at or near puberty and irregular menses from the age of menarche because of oligo-ovulation or anovulation.** Clinical manifestations are as follows: .

- **Affected girls may be but are not necessarily somewhat overweight.**
- **In rare instances, menarche may be delayed, and primary amenorrhea also may occur.**
- **Basal levels of LH tend to be elevated in most affected individuals, and androgen production is invariably increased, even though circulating levels of androgens may be near the upper limits of the normal range in many affected women.**
- **In anovulatory women, estrone levels are typically greater than estradiol levels.**
-

Because circulating levels of estrogens are not diminished in PCOS and androgen levels are only mildly elevated, affected girls become both feminized and masculinized at puberty. This is an important feature because girls with classic forms of CAH who do not experience precocious puberty (and even those who do) only become masculinized at puberty (i.e., they do not develop breasts).

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- Some degree of insulin resistance may be present, even in the absence of overt glucose intolerance (72).
- Polycystic ovaries are frequently, but not always present in ultrasound examination.





Figure 26.21 Typical facial hirsutism in 3 women with polycystic ovarian syndrome. A: 25 year-old. B: 21 year-old C: 17 year-old.

Differential Diagnosis and Evaluation

Distinguishing PCOS from the nonclassic forms of CAH is problematic and controversial (73,74). The evaluation is as follows:.

- **Some clinicians advocate measurement of 17 α -hydroxyprogesterone in all women who develop hirsutism.** Although values of 17 α -hydroxyprogesterone are commonly elevated more than 100-fold in individuals with classic 21-hydroxylase deficiency, they may or may not be elevated in nonclassic late-onset forms of the disorder.
 - **Measurement of 17 α -hydroxyprogesterone also can identify women with various forms of 11-hydroxylase deficiency..**
 - **Basal levels of DHEAS as well as 17 α -hydroxyprogesterone may be moderately elevated in patients with PCOS, making the diagnosis even more difficult.**
-
- **To screen for CAH, 17 α -hydroxyprogesterone should be measured in early morning..**
 - **In women with regular cyclic menses, it is important to measure 17 α -hydroxyprogesterone only in the follicular phase because basal levels increase at midcycle and in the luteal phase..**

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Measurements of 17 α -hydroxyprogesterone appear to be of value in populations at high risk for nonclassic late-onset 21-hydroxylase deficiency. In the white population, the gene occurs in only about 1 in 1,000 individuals, but it occurs in 1 in 27 Ashkenazi Jews, 1 in 40 Hispanics, 1 in 50 Yugoslavs, and 1 in 300 Italians (67). The incidence is also increased among Eskimos and French Canadians. Alternatively, screening might be restricted to hirsute teenagers presenting with the more "typical" features of nonclassic 21-

the breasts (i.e., defeminization), shorter stature than other family members, and increased DHEAS levels (between 5,000 and 7,000 ng/mL). Women with a strong family history of hirsutism or hypertension might be screened as well (41) (Fig. 26.22).

Basal Levels of 17 α -Hydroxyprogesterone

Basal levels of 17 α -hydroxyprogesterone higher than 800 ng/dL are virtually diagnostic of CAH. Levels between 300 and 800 ng/dL require stimulatory testing with corticotropin to distinguish between PCOS and CAH. To complicate the situation even further, nonclassic 21-hydroxylase deficiency may occur even when basal levels of 17 α -hydroxyprogesterone are below 300 ng/dL, thus requiring stimulatory testing in those cases as well..

Cosyntropin Stimulation Test

The most commonly used stimulatory test involves measurement of 17 α -hydroxyprogesterone 30 minutes after administration of a bolus of 250 mg of synthetic cosyntropin (*Cortrosyn*) (75). In normal women, this value seldom exceeds 400 ng/dL. Patients with classic 21-hydroxylase deficiency achieve peak levels of 3,000 ng/dL or higher. Patients with nonclassic 21-hydroxylase deficiency commonly achieve levels of 1,500 ng/dL or more. Heterozygous carriers achieve peak levels up to about 1,000 ng/dL. In hirsute women with hypertension, 11-deoxycortisol levels can be determined during the test. If both 11-deoxycortisol and 17 α -hydroxyprogesterone levels are increased, the rare 11-hydroxylase deficiency is present. Only measurements of several steroid precursors after corticotropin stimulation can identify individuals with nonclassic forms of 3 β -HSD deficiency.

The elevated levels of 17 α -hydroxyprogesterone present in all forms of 21-hydroxylase deficiency are rapidly suppressed by administration of exogenous corticoids. Even a single dose of a glucocorticoid such as *dexamethasone* will suppress 17 α -hydroxyprogesterone in CAH but not in virilizing ovarian and adrenal neoplasms.

Hirsutism

It has been suggested that androgen-receptor blockade may be preferable to glucocorticoids as primary treatment of nonclassic 21-hydroxylase deficiency (76). Although menses usually (but not always) become regular shortly after beginning therapy with glucocorticoids, the hirsutism in this disorder has proved to be remarkably refractory to glucocorticoids.

Distinguishing nonclassic forms of CAH from idiopathic hirsutism also may be problematic. Individuals with idiopathic hirsutism have regular ovulatory menses, thus effectively eliminating PCOS from consideration. Confusion can be created by the fact that some women with nonclassic CAH may continue to ovulate. Basal levels of 17 α -hydroxyprogesterone are normal in idiopathic hirsutism, as is the response to adrenocorticotrophic hormone stimulation. Idiopathic hirsutism represents enhanced androgen action at the hair follicle (77).

Mixed Gonadal Dysgenesis

The term *mixed gonadal dysgenesis* is used to designate those individuals with asymmetric gonadal development, with a germ cell tumor or a testis on one side and an undifferentiated streak, rudimentary gonad, or no gonad on the other side.

Most individuals with this rare disorder have a mosaic karyotype of 45,X/46,XY and are raised as girls who then experience virilization at puberty. Gonadectomy is indicated to remove the source of androgens and eliminate any risk for neoplasia.

Rare Forms of Male Pseudohermaphroditism

Individuals who have rare forms of male pseudohermaphroditism, especially 5 α -reductase deficiency (the so-called *penis at 12 syndrome*) and the *Reifenstein syndrome*, generally have ambiguous female genitalia with variable virilization at puberty. *Cushing syndrome*, too, may occur rarely during the pubertal years, as may adrenal or ovarian androgen-secreting neoplasms.



Figure 26.22 A 19-year-old girl with secondary amenorrhea and severe acne and hirsutism beginning at the normal age of puberty. Stimulatory testing with corticotropin documented nonclassic 21-hydroxylase deficiency. Flattening of the breasts is apparent. She was shorter than her one sister and her mother.



Figure 26.23 Newborn girl with 46,XX karyotype and genital ambiguity. There is obvious clitoral hypertrophy, paired frenula, so-called scrotalization of the labia, and a common urogenital sinus (shown by the probe). She had 21-hydroxylase deficiency. (From **Rebar RW**. Normal and abnormal sexual differentiation and pubertal development. In: **Moore TR, Reiter RC, Rebar RW, et al**, eds. *Gynecology and obstetrics: a longitudinal approach*. New York, NY: Churchill Livingstone, 1993:97–133, with permission.)

Genital Ambiguity at Birth

Because of the concerns of the parents and the need to prevent life-threatening complications, the infant with genital ambiguity should be evaluated promptly. Evaluation and treatment is best conducted by a team of physicians.

The initial evaluation is as follows:.

- **Cytogenetic and endocrine studies should be initiated promptly.** Use of specific probes for the Y chromosome and fluorescent *in situ* hybridization can assist in obtaining a karyotype within 48 hours. Probes for many specific inherited disorders are now available.
- **To exclude CAH, the most common cause of genital ambiguity, serum levels of sodium, potassium, and 17 α -hydroxyprogesterone and urinary excretion of 17-ketosteroids, pregnanetriol, and tetrahydrodeoxycortisol should be measured.** Infants should be monitored closely to prevent development of dehydration, hyponatremia, and hyperkalemia.
- **It has been suggested that antimüllerian hormone be measured in infants with**

genital ambiguity because it is elevated in boys and undetectable in girls in the first several years of life (78).

Table 26.3 Androgens and Progestogens Potentially Capable of Producing Genital Ambiguity^a

Proved	No Effect	Insufficient Data
<i>Testosterone enanthate</i>	<i>Progesterone</i>	<i>Ethinodiol diacetate</i>
<i>Testosterone propionate</i>	<i>17α-Hydroxyprogesterone</i>	<i>Dimethisterone</i>
<i>Methylandrostenediol</i>	<i>Medroxyprogesterone</i>	<i>Norgestrel</i>
<i>6α-Methyltestosterone</i>	<i>Norethynodrel</i>	<i>Desogestrel</i>
<i>Ethisterone</i>		<i>Gestodene</i>
<i>Norethindrone</i>		<i>Norgestimate</i>
<i>Danazol</i>		

^a Those agents proved to cause genital ambiguity do so only when administered in relatively high doses. Insufficient data exist regarding effects of *dimethisterone* and *norgestrel*. In low doses (e.g., as in oral contraceptives), progestins, even including *norethindrone*, seem unlikely to virilize a female fetus.

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Physical Signs

During the 3 to 4 days required for evaluation, it is important to be supportive of the parents. Many clinicians believe that it is important not to attach any unusual significance to the genital ambiguity and to treat the abnormality as just another "birth defect." Physicians should emphasize that the child should undergo normal psychosexual development regardless of the sex-of-rearing selected. Either a name compatible with either sex should be chosen, or the naming of the infant should be delayed until the studies have been completed.

Although the diagnosis is not usually obvious on examination, there are some helpful distinguishing features (Fig. 26.23). **In normal boys, there is only a single midline frenulum on the ventral side of the phallus; in normal girls, there are two frenula lateral to the midline. A girl with clitoral enlargement still has two frenula, and a boy with hypospadias has a single midline frenulum or several irregular fibrous bands (chordee).** It is important to determine whether any müllerian derivatives are present. Recent studies suggest that MRI may be the most effective way of evaluating the infant for the presence of müllerian tissue (79).

The location or consistency of the gonad may be helpful in deducing its composition. A gonad located in the labial or inguinal regions almost always contains testicular tissue. A testis is generally softer than an ovary or a streak gonad and is more apt to be surrounded by blood vessels imparting a reddish cast. An ovary is more often white, fibrous, and convoluted. A gonad that varies in consistency may be an ovotestis or a testis or a streak gonad that has undergone neoplastic transformation. If a well-differentiated fallopian tube is absent on only one side, the side without the tube probably contains a testis or ovotestis.

Diagnosis and Management

Although genital ambiguity is usually identified at birth, it may not be recognized for several years. Questions about changing the sex-of-rearing may arise. It has been believed that sex-of-rearing may be changed before 2 years of age without

psychologically damaging the child, but experience with individuals with 5 α -reductase deficiency suggests that gender changes may be made after 2 years of age in certain instances (80). In any case, **surgery for genital ambiguity to make the external genitalia (and development) as compatible with the sex-of-rearing of the child is warranted but has not always been successful.** Clitoral recession and clitorrectomy are the most frequently performed surgical procedures.

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It is possible to diagnose 21-hydroxylase deficiency prenatally in patients known to be at risk (67). The diagnosis is established by documenting elevated levels of 17 α -hydroxyprogesterone or 21-deoxycortisol in amniotic fluid. Genetic diagnosis using specific probes and cells obtained by chorionic villus sampling or amniocentesis also is possible. Prenatal treatment of the fetus by administering *dexamethasone* to the mother is usually but not always successful in preventing genital ambiguity (81). Moreover, maternal complications, including hypertension, massive weight gain, and overt Cushing syndrome, have been noted in about 1% of pregnancies in which the mothers are given low doses of *dexamethasone*. Despite the risks and the nonuniformity of beneficial outcome to affected female fetuses, many parents may choose prenatal medical treatment because of the psychological impact of ambiguous genitalia.

Teratogens

It is important to recognize that ambiguous genitalia can result from the maternal ingestion of various teratogens, most of which are synthetic steroids (Table 26.3). Exposure to the teratogen must occur early in pregnancy, during genital organogenesis. Moreover, not all exposed fetuses manifest the same anomalies or even the presence of any anomalies. In principle, most synthetic steroids with androgenic properties, including weakly androgenic progestins, can affect female genital differentiation. However, the doses required to produce genital ambiguity are generally so great that the concern is only theoretical. The one agent that clearly can lead to genital ambiguity when ingested in clinically used quantities is *danazol*. There is no evidence that inadvertent ingestion of oral contraceptives, which contain relatively low doses of either *mestranol* or *ethinyl estradiol* and a 19-nor-steroid, results in virilization **(82,83)**..

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27

Amenorrhea

Wendy J. Schillings

Howard D. McClamrock



- **Girls have experienced menarche at increasingly younger ages during the past century. To continue to represent two standard deviations above the mean age for development of secondary sexual characteristics and menses, respectively, the age limitations defining primary amenorrhea have been lowered. Primary amenorrhea is now defined as absence of menses at age 13 years when there is no visible secondary sexual characteristic development or age 15 years in the presence of normal secondary sexual characteristics.**
- **When premature gonadal failure occurs in conjunction with primary amenorrhea, it is associated with a relatively high incidence of genetic abnormalities (30%).**
- **The anatomic causes of amenorrhea are relatively few, and the majority may be diagnosed by history and physical examination.**
- **The most important elements in the diagnosis of amenorrhea include physical examination for secondary sexual characteristics and anatomic abnormalities measurement of human chorionic gonadotropin (hCG)**

to rule out pregnancy, and assessment of follicle-stimulating hormone (FSH) levels to differentiate between hypergonadotropic and hypogonadotropic forms of hypogonadism.

- **Therapeutic measures may include specific therapies (medical or surgical) aimed at correcting the primary cause of amenorrhea, hormone replacement to initiate and maintain secondary sexual characteristics and provide symptomatic relief, treatments aimed at maintenance of bone mass (bisphosphonates), and ovulation induction for patients desiring pregnancy.**

A complex hormonal interaction must take place in order for normal menstruation to occur. The hypothalamus must secrete gonadotropin-releasing hormone (GnRH) in a pulsatile fashion, which is modulated by neurotransmitters and hormones. The GnRH stimulates secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, which promotes ovarian follicular development and ovulation. A normally functioning ovarian follicle secretes estrogen; after ovulation, the follicle is

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converted to a corpus luteum, and progesterone is secreted in addition to estrogen. These hormones stimulate endometrial development. If pregnancy does not occur, estrogen and progesterone secretion decrease, and withdrawal bleeding begins. If any of the components (hypothalamus, pituitary, ovary, outflow tract, and feedback mechanism) are nonfunctional, bleeding cannot occur. Amenorrhea occurs in 3% to 4% of reproductive age women who are not pregnant.

The mean age of menarche has become younger during this century. Therefore, the definition has changed: Primary amenorrhea is defined as the absence of menses by 13 years of age when there is no visible secondary sexual characteristic development or by 15 years of age in the presence of normal secondary sexual characteristics. It has been adjusted by 1 year to continue to represent two standard deviations above the mean age of developing secondary sexual characteristics and menses, respectively (1). A woman who has previously menstruated can develop secondary amenorrhea, which is defined as absence of menstruation for three normal menstrual cycles or 6 months (2).

Patients may develop slight alterations in the hypothalamic-pituitary-ovarian axis that are not severe enough to cause amenorrhea but instead cause anovulation. Anovulatory patients usually have irregular menses and may bleed excessively during menstruation because estrogen is unopposed. This often occurs at the beginning and end of the reproductive years. Luteal phase defect is caused by minimal alterations in the hypothalamic-pituitary-ovarian axis, and patients have regular menses along with infertility or recurrent pregnancy loss. Except for anatomic and chromosomal etiologies, luteal phase defects and anovulation have causes similar to those of amenorrhea, but the hypothalamic, pituitary, or ovarian hormonal dysfunction is less severe or of shorter duration than with amenorrhea.

To detect the cause of amenorrhea, it is useful to determine whether secondary sexual characteristics are present (Fig. 27.1). The absence of secondary sexual characteristics indicates that a woman has never been exposed to estrogen stimulation..

Amenorrhea without Secondary Sexual Characteristics

Although the diagnosis and treatment of disorders associated with hypogonadism

have been discussed in another chapter, they also will be mentioned here because these conditions may present as primary amenorrhea. Because breast development is the first sign of estrogen exposure in puberty, patients without secondary sexual characteristics have primary not secondary amenorrhea. The absence of a uterus suggests certain enzyme deficiencies (see Fig 27.1) and indicates the presence of antimüllerian hormone (AMH) in an XY individual. Because these conditions are very rare, it is easier to categorize the causes of amenorrhea in the absence breast development on the basis of gonadotropin status.

Causes of Primary Amenorrhea

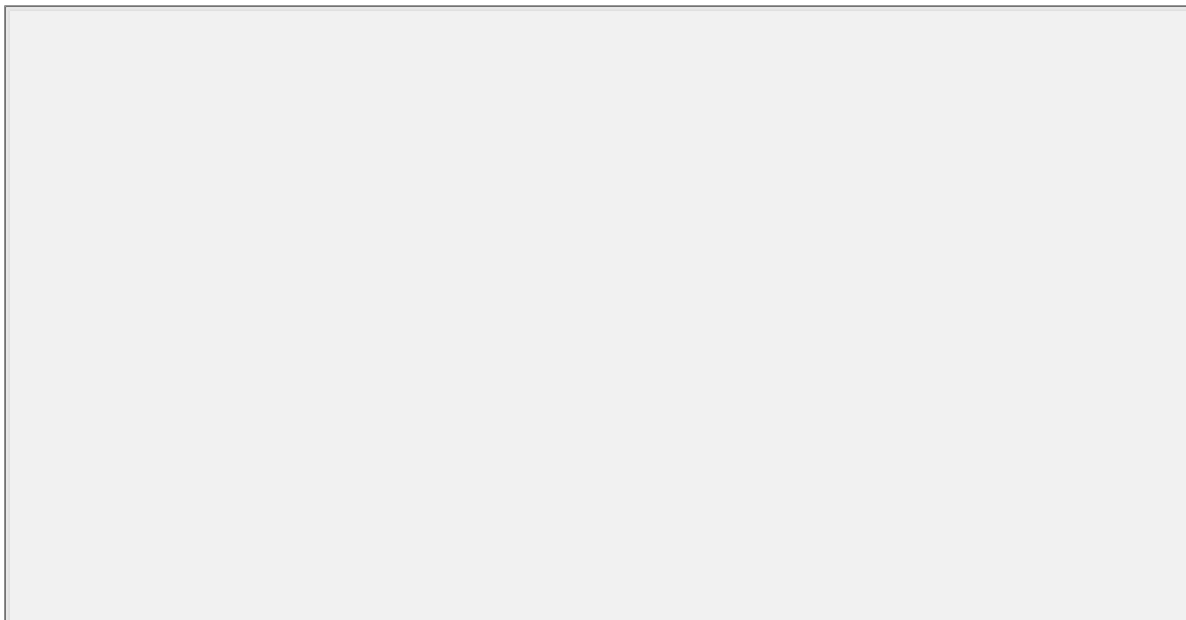
Hypergonadotropic Hypogonadism

Primary gonadal failure and the resulting impaired secretion of gonadal steroids are manifested by elevated levels of LH and FSH that arise from decreased negative feedback. Gonadal failure as well as primary amenorrhea are most often associated with genetic abnormalities (Table 27.1). Approximately 30% of patients with primary amenorrhea

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have an associated genetic abnormality (3). The syndrome of gonadal dysgenesis, or Turner syndrome, and its variants represent the most common form of hypogonadism in women (see Chapter 26). **Other disorders associated with primary amenorrhea include structurally abnormal X chromosomes, mosaicism, pure gonadal dysgenesis (46,XX and 46,XY with gonadal streaks), enzyme deficiencies that prevent normal estrogen production, and gonadotropin–receptor inactivating mutations. Individuals with these conditions have gonadal failure and cannot synthesize ovarian steroids. Therefore, gonadotropin levels are elevated because of the lack of negative estrogen feedback on the hypothalamic–pituitary axis.** Most patients with these conditions have primary amenorrhea and lack secondary sexual characteristics. **However, occasionally patients with a partial deletion of the X chromosome, mosaicism, or pure gonadal dysgenesis (46,XX) may synthesize enough estrogen in early puberty to induce breast development and a few episodes of uterine bleeding. Ovulation and, occasionally, pregnancy are possible..**



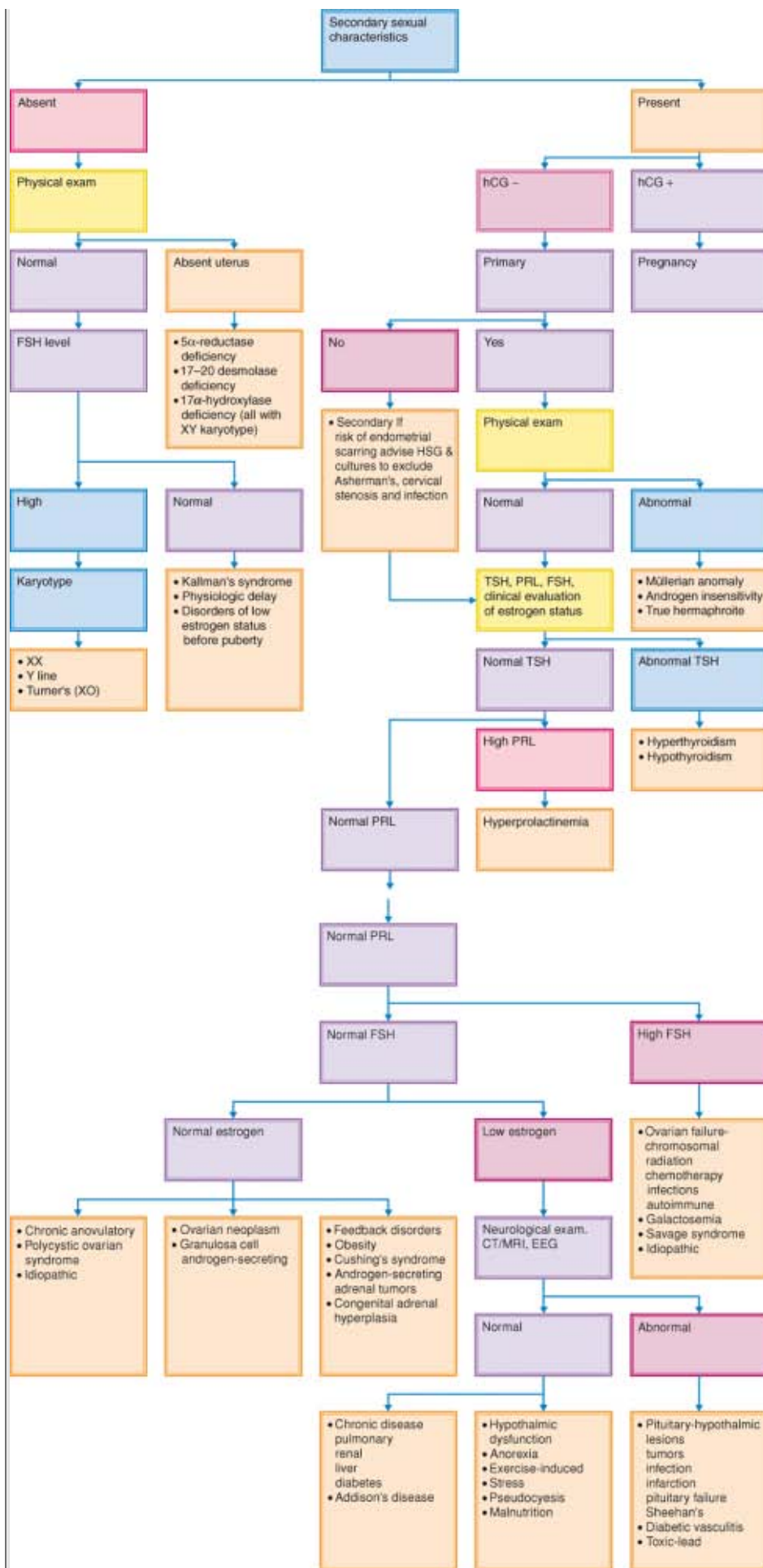


Figure 27.1 Decision tree for evaluation of amenorrhea. FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; HSG, hysterosalpingogram; TSH, thyroid-stimulating hormone; PRL, prolactin; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram.

Table 27.1 Amenorrhea Associated with a Lack of Secondary Sexual Characteristics

Abnormal physical examination

5 α -reductase deficiency in XY individual

17, 20-desmolase deficiency in XY individual

17 α -hydroxylase deficiency in XY individual

Hypergonadotropic hypogonadism

Gonadal dysgenesis

Pure gonadal dysgenesis

Partial deletion of X chromosome

Sex chromosome mosaicism

Environmental and therapeutic ovarian toxins

17 α -hydroxylase deficiency in XX individual

Galactosemia

Other

Hypogonadotropic hypogonadism

Physiologic delay

Kallmann's syndrome

Central nervous system tumors

Hypothalamic/pituitary dysfunction

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Genetic Disorders

Gonadal Dysgenesis

It appears that patients with Turner syndrome initially have normal ovarian development. Amenorrhea is the result of accelerated atresia of the follicles. The fibrotic ovaries are called streak ovaries.

Abnormal X Chromosome

46,XX individuals with partial deletions of the X chromosome have variable phenotypes depending on the amount and location of the missing genetic material.

Patients with a deletion of the long arm of the X chromosome (Xq-) from Xq13 to Xq26 have sexual infantilism, normal stature, no somatic abnormalities, and streak gonads (6,7).

Some patients may be eunuchoid in appearance and have delayed epiphyseal closure. Patients with a deletion of the short arm of the X chromosome (Xp) usually are phenotypically similar to individuals with Turner syndrome (8). Many genes on the Xp chromosome escape X inactivation and act similarly to genes on autosomes. The effective monosomy created by the deletion results in the phenotypic

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features of Turner syndrome (5). Most patients with a ring X have ovarian failure and phenotypes similar to Turner syndrome, although some have been able to reproduce successfully. These patients differ from those with Turner syndrome in that they are more likely to be mentally retarded and have syndactyly. Patients with isochromosome of the long arm of the X chromosome ($i[Xq]$) are also similar to XO patients, with the exception that autoimmune disorders are more common. Half of the women with balanced translocations of the X chromosome to an autosome have gonadal failure. Typically, the normal X is inactivated to preserve the balance of autosomal genes. The gonadal failure can be caused by the chromosomal break occurring in a gene that is required for ovarian function, abnormal meiosis, or X inactivation of the translocated X and adjacent autosomal genes (5,9).

Mosaicism

Primary amenorrhea is associated with various mosaic states, the most common of which is 45,X/46,XX (10). As discussed in Chapter 26, the clinical findings in 45,X/47,XXX and 45,X/46,XX/47,XXX are similar to those in 45,X/46,XX and vary in estrogen and gonadotropin production, depending on the number of follicles in the gonads. When compared with the pure 45,X cell line, individuals with 45,X/46,XX are taller and have fewer abnormalities, although 80% of those with 45,X/46,XX mosaics are shorter than their peers, and 66% have some somatic abnormalities. Spontaneous menstruation occurs in approximately 20% of these patients (10).

Pure Gonadal Dysgenesis

Individuals who are phenotypically female with sexual infantilism, primary amenorrhea, normal stature, and no chromosomal abnormalities (46,XX or 46,XY) have pure gonadal dysgenesis The gonads are usually streaks, but there may be some development of secondary sexual characteristics, as well as a few episodes of uterine bleeding.

Swyer syndrome occurs when mutations in the SRY (sex-determining region gene on the Y chromosome) located at Yp11 result in XY females with gonadal dysgenesis (11,12). This explains 15% to 20% of women who are 46,XY. Most of the mutations in SRY cause abnormalities in the DNA-binding domain (the human menopausal gonadotropin box) of the protein (13).

Mutations in other genes such as SOX9, DAX1, WT-1, and SF 1, which affect testicular differentiation and inhibit antimüllerian hormone production, also result in XY pure gonadal dysgenesis. The SOX9 gene located at 17q24 has a role in testis differentiation and promotes antimüllerian hormone secretion. Some but not all mutations in the SOX9 gene are known to cause XY sex reversal, along with campomelic dysplasia (severe skeletal abnormalities) (14,15). Duplications of the DAX 1 gene at Xp21 cause dose-sensitive XY sex reversal (16). DAX 1 is hypothesized to antagonize the SRY gene, preventing testis development. Transgenic XY mice with overexpression of the DAX 1 gene develop as phenotypic females, supporting this hypothesis (13). Mutation in the WT 1 gene (Wilms' tumor suppressor gene 1) located at 11p13 causes several different syndromes, depending on where the mutation in the gene occurs. In Frasier syndrome, there is alternative splicing, which causes the protein product to lack a highly conserved KTS triplet repeat. The normal +KTS isoform of the protein is believed to synergize with SF 1 (steroidogenic factor 1) to promote the expression of antimüllerian hormone. Lack of the +KTS isoform in an XY patient results in normal female internal and external genitalia, streak gonads, and progressive glomerulopathy. **These women frequently develop gonadoblastomas but rarely develop Wilms' tumor, which is associated with mutations in other locations in the WT 1 gene.** XX patients with the mutation that prevents the +KTS isoform have similar

kidney abnormalities but develop normal ovaries and genitalia (13,17,18). One XY patient with a heterozygous mutation of the *SF 1* gene had adrenal failure and sex reversal (19). *SF 1* is an orphan nuclear receptor that not only regulates AMH expression but also regulates all the cytochrome P450 steroid hydroxylase enzymes (18).

Duplication of 1p, which encodes the *WNT 4* gene, has caused XY sex reversal. *WNT 4* may upregulate DAX 1 transcripts. A TRX mutation has also caused XY sex reversal. Other genes that cause XY gonadal dysgenesis are likely to be identified in the future. Mutations at 9p24 and 10q cause XY sex reversal, but the exact genes causing the defects have not yet been elucidated (13,18,20).

XX pure gonadal dysgenesis can be caused by the presence of small Y chromosome fragments in their genome. It is estimated that 5% to 40% of patients with Ullrich–Turner syndrome were found to have Y sequences by polymerase chain reaction (PCR), depending on the DNA sequences targeted for testing (21,22). If Y sequences are present, gonadectomy is advised because of the risk of gonadoblastoma (21). In other patients with XX gonadal dysgenesis, the condition is likely to be caused by genes that lead to ovarian failure before pubertal development, resulting in streak gonads. Genes that cause ovarian failure are discussed later in this chapter.

Mixed Gonadal Dysgenesis

Most patients are XY and have ambiguous genitalia with a streak gonad on one side and a malformed testis on the opposite. A small proportion of these patients have mutations in the *SRY* gene (13).

Enzyme Deficiencies

Congenital Lipoid Adrenal Hyperplasia

Patients with this autosomal recessive disorder are unable to convert cholesterol to pregnenolone, which is the first step in steroid hormone biosynthesis. A defect has not been found in the *P450scc* gene, which is the conversion enzyme responsible for this step in the pathway. Instead, 15 different mutations have been identified in the steroidogenic acute regulatory protein (StAR), which facilitates the transport of cholesterol from the outer to the inner mitochondrial membrane. This protein appears to be the rate-limiting step for steroid hormone biosynthesis stimulated by tropic hormones. These patients present in infancy with hyponatremia, hyperkalemia, and acidosis. Both XX and XY individuals are phenotypically female. Genetic clusters of the disorder are found in the Japanese/Korean and Palestinian Arab populations. With appropriate mineralocorticoid and glucocorticoid replacement, these patients can survive into adulthood. Most patients are XY and do not have a uterus. Without hormone replacement, they remain sexually infantile. XX patients may acquire secondary sexual characteristics at puberty but develop large ovarian cysts and early ovarian failure as a result of accumulation of cholesterol in the ovaries (23,24).

17 α -Hydroxylase and 17,20-Desmolase Deficiency

Mutations in the *CYP17* gene cause abnormalities in both the **17 α -hydroxylase and 17,20-desmolase functions of the protein that is active in the adrenal and gonadal steroidogenic pathways.** More than 20 mutations that alter the reading frame of the gene have been identified, even though fewer than 200 people have the disorder (25).

Patients have either 46,XX or 46,XY karyotypes. The uterus is absent in individuals with 46,XY karyotype, a feature distinguishing them from individuals with 46,XX karyotype. Individuals with CYP17 mutations have primary amenorrhea, no secondary sexual characteristics, female phenotype, hypertension, and hypokalemia (26). The diminished levels of 17 α -hydroxylase that characterize this disorder lead to a reduction in cortisol production, which in turn causes an increase in adrenocorticotrophic hormone (ACTH). 17 α -hydroxylase is not required for production of mineralocorticoids; thus, excessive amounts of mineralocorticoid are produced, resulting in sodium retention, loss of potassium, and hypertension. Patients with **17 α -hydroxylase deficiency have primordial follicles, but gonadotropin levels are elevated because the enzyme deficiency prevents synthesis of sex steroids.**

Aromatase Deficiency

This rare autosomal recessive abnormality, which has only been reported in six cases, prevents the affected individual from aromatizing androgens to estrogen. **This syndrome may be suspected even before birth because most mothers of**

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affected children also become virilized during pregnancy. This occurs because the placenta cannot convert the fetal androgens to estrogen, and they are diffused into the maternal circulation. At birth, a female child has clitoromegaly and posterior labioscrotal fusion. At puberty, there is no breast development, primary amenorrhea, worsening virilization, absent growth spurt, delayed bone age, and multicystic ovaries. The diagnostic hormonal pattern consists of an elevation of FSH, LH, testosterone, and dehydroepiandrosterone sulfate (DHEAS) levels, and undetectable levels of estradiol. Estrogen therapy has been shown to improve the ovarian and skeletal abnormalities but must be titrated to mimic normal estrogen levels. Therefore, amounts given should be minimal during childhood and then increased at puberty (27,28).

Gonadotropin Receptor Mutations

Luteinizing Hormone Receptor Mutation

Inactivation of LH receptors has been identified in XY pseudohermaphrodites with primary amenorrhea in the absence of secondary sexual characteristics caused by homozygous premature stop codon, deletions, and missense mutations in the LHR gene located on chromosome 2. The Leydig cells in these individuals are unable to respond to LH, causing Leydig cell hypoplasia. This leads to early testicular failure and prevents masculinization. XX siblings with the same mutations develop normal secondary sexual characteristics but are amenorrheic with elevated LH levels, normal FSH levels, and cystic ovaries (29,30).

Follicle-Stimulating Hormone Receptor Mutation

An autosomal recessive single amino acid substitution in the extracellular domain of the FSH receptor, which prevents FSH binding, has been identified in six families in Finland. This condition leads to primary or early secondary amenorrhea, variable development of secondary sexual characteristics, and high levels of FSH and LH (31).

Other Causes of Primary Ovarian Failure

Amenorrhea and premature ovarian failure can occur in association with irradiation of the ovaries (32), chemotherapy with alkylating agents (e.g., cyclophosphamide) (33), or combinations of radiation and other chemotherapeutic agents. In girls, galactosemia often

is associated with premature ovarian failure, but it usually is detected by newborn screening programs. **Gonadotropin resistance, autoimmune ovarian failure, and ovarian failure resulting from infectious and infiltrative processes have also been described.**

Hypogonadotropic Hypogonadism

Primary amenorrhea resulting from hypogonadotropic hypogonadism occurs when the hypothalamus fails to secrete adequate amounts of GnRH or when a pituitary disorder associated with inadequate production or release of pituitary gonadotropins is present.

Physiologic Delay

Physiologic or constitutional delay of puberty is the most common manifestation of hypogonadotropic hypogonadism. Amenorrhea may result from the lack of physical development caused by delayed reactivation of the GnRH pulse generator.

Levels of GnRH are functionally deficient in relation to chronologic age but normal in terms of physiologic development.

Kallmann Syndrome

The second most common hypothalamic cause of primary amenorrhea associated with hypogonadotropic hypogonadism is insufficient pulsatile secretion of GnRH (Kallmann syndrome), which has varied modes of genetic transmission, as discussed in Chapter 26. Insufficient pulsatile secretion of GnRH leads to deficiencies in FSH and LH. Deficiencies in GnRH may also be caused by developmental or genetic defects, inflammatory processes, tumors, vascular lesions, or trauma. Patients with isolated deficiencies of LH and FSH usually are a normal height for their age, whereas

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patients with physiologic delay of puberty are usually short for their chronologic age but normal for their bone age (34).

Central Nervous System Tumors

Central nervous system tumors that lead to primary amenorrhea, the most common of which is craniopharyngioma, are usually extracellular masses that interfere with the synthesis and secretion of GnRH or stimulation of pituitary gonadotropins. Virtually all of these patients have disorders in the production of other pituitary hormones as well as LH and FSH (35,36). Prolactin-secreting pituitary adenomas are rare in childhood and more commonly occur after development of secondary sexual characteristics.

Genetic Disorders

5 α -Reductase Deficiency

5 α -Reductase deficiency should also be considered as a cause of amenorrhea (37). Patients with this disorder are genotypically XY, frequently experience virilization at puberty, have testes (because of functioning Y chromosomes), and have no müllerian structures as a result of functioning AMH. 5 α -Reductase converts testosterone to its more potent form, dihydrotestosterone. **Patients with 5 α -reductase deficiency differ from patients with androgen insensitivity because they do not develop breasts at puberty. These patients have**

low gonadotropin levels as a result of testosterone levels that are sufficient to suppress breast development and allow normal feedback mechanisms to remain intact. Normal male differentiation of the urogenital sinus and external genitalia do not occur because dihydrotestosterone is required for this development. However, normal internal male genitalia derived from the wolffian ducts are present because this development requires only testosterone. Male pattern hair growth, muscle mass, and voice deepening are also testosterone dependent.

Gonadotropin-releasing Hormone Receptor Mutations

Several mutations have been identified in the GnRH receptor gene that cause abnormal GnRH function. Most affected patients are compound heterozygotes, but homozygous autosomal recessive mutations have also been identified. The GnRH receptor is a G-protein-coupled receptor. Functional studies show that the mutations either cause marked decrease in binding of GnRH to its receptor or prevent second-messenger signal transduction. Without a functional signal transduction, FSH and LH are not stimulated and are unable to promote follicular growth (38). All patients are normosomic. **Receptor mutations in GnRH cause 17% of sporadic cases of idiopathic hypogonadotropic hypogonadism with normal olfaction** (39).

Follicle-stimulating Hormone Deficiency

Patients with FSH deficiency usually seek treatment for delayed puberty and primary amenorrhea caused by hypoenestrogenism. They are distinguished from other hypoenestrogenic patients by having decreased FSH levels and increased LH levels. These patients have low serum androgen levels despite the abnormal LH-to-FSH ratio, indicating that FSH-stimulated follicular development is a prerequisite for thecal cell androgen production. In some of these patients, autosomal recessive mutations in the FSH β subunit, which impair dimerization of α and β subunits and prevent binding to the FSH receptor, have been identified (40). Pregnancy was achieved in one patient after induction of ovulation with injectable gonadotropins (41).

Other Hypothalamic/Pituitary Dysfunctions

Functional gonadotropin deficiency results from malnutrition, malabsorption, weight loss or anorexia nervosa, excessive exercise, chronic disease, neoplasias, and marijuana use (42,43,44,45,46). Hypothyroidism, polycystic ovarian syndrome (PCOS), Cushing syndrome, hyperprolactinemia, and infiltrative disorders of the central nervous system are rare causes of primary amenorrhea (47,48). Constitutional delay without

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underlying causes is less common in girls than in boys, and the reason for lack of development should be vigorously pursued (49).

Diagnosis

A careful history and physical examination are necessary to appropriately diagnose and treat primary amenorrhea associated with hypogonadism. The physical examination may be particularly helpful in patients with Turner syndrome. A history of short stature but consistent growth rate, a family history of delayed puberty, and normal physical findings (including assessment of smell, optic disks, and visual fields) may suggest physiologic delay. Headaches, visual disturbances, short stature, symptoms of diabetes insipidus, and weakness of one or more limbs suggest central nervous system lesions (36). Galactorrhea may be seen with prolactinomas. The history of galactorrhea may provide helpful information in

the diagnosis of postinfectious, inflammatory, or vascular lesions of the central nervous system; trauma; anorexia nervosa; stress-related amenorrhea; or other systemic disease process.

The diagnostic workup is summarized as follows: .

- **The initial laboratory test should be assessment of serum FSH levels unless the history and physical examination suggest otherwise.** The FSH level differentiates hypergonadotropic and hypogonadotropic forms of hypogonadism. If the FSH level is elevated, a karyotype should be obtained. An elevated FSH level in combination with a 45, X karyotype confirms the diagnosis of Turner syndrome. Partial deletion of the X chromosome, mosaicism, pure gonadal dysgenesis, and mixed gonadal dysgenesis are diagnosed by obtaining a karyotype.
- **Because of the association with coarctation of the aorta (up to 30%) and thyroid dysfunction, patients with Turner syndrome should undergo echocardiography every 3 to 5 years and thyroid function studies yearly.** They should also be evaluated for hearing loss and hypertension.
- **If the karyotype is abnormal and contains the Y chromosome, as in gonadal dysgenesis, the gonads should be removed to prevent tumors.** Patients should also be screened for nephrotic syndrome, which can occur in Frasier syndrome.
- **If the karyotype is normal and the FSH level is elevated, it is important to consider the diagnosis of 17 α -hydroxylase deficiency because it may be a life-threatening disease if untreated.** This diagnosis should be considered when testing indicates elevated serum progesterone (>3.0 ng/mL) levels, a low 17 α -hydroxyprogesterone (0.2 ng/mL) level, and an elevated serum deoxycorticosterone level (DOS) (50). The diagnosis is confirmed with an ACTH stimulation test. After ACTH bolus administration, affected individuals have markedly increased levels of serum progesterone compared with baseline levels and no change in serum 17 α -hydroxyprogesterone levels.
- **If the screening FSH level is low, the diagnosis of hypogonadotropic hypogonadism is established..**
- **Central nervous system lesions should be ruled out by imaging using computed tomography (CT) or magnetic resonance imaging (MRI), especially if galactorrhea, headaches, or visual field defects are identified.** Suprasellar or intrasellar calcification in an abnormal sella is found in approximately 70% of patients with craniopharyngioma (36).

- **Physiologic delay is a diagnosis of exclusion that is difficult to distinguish from insufficient GnRH secretion.** The diagnosis can be supported by a history suggesting physiologic delay, an x-ray showing delayed bone age, and the absence of a central nervous system lesion on computed tomography (CT) or MRI scanning.
- **Gonadotropin-deficient patients can usually be distinguished from patients**

with physiologic delay by their response to GnRH stimulation. Patients with physiologic delay have a normal LH response to GnRH stimulation for their bone age, in contrast with gonadotropin-deficient patients, in whom the LH and FSH responses are low (51).

Treatment of Amenorrhea

Individuals with primary amenorrhea associated with all forms of gonadal failure and hypergonadotropic hypogonadism need cyclic estrogen and progestin therapy to initiate, mature, and maintain secondary sexual characteristics. Prevention of osteoporosis is an additional benefit of estrogen therapy:

- **Therapy is usually initiated with 0.625 mg/day of conjugated estrogens or 1 mg/day of estradiol.**
- **If the patient is short in stature, higher doses should not be used in an attempt to prevent premature closure of the epiphyses.** Most of these patients are of normal height, however, and higher estrogen doses may be used initially and then reduced to the maintenance doses after several months.
- **Estrogen can be given daily in combination with progestin (*medroxyprogesterone acetate*) or progesterone to prevent unopposed estrogen stimulation of the endometrium in patients with a uterus.** *Medroxyprogesterone acetate* may be administered at a dose of 2.5 mg daily or 5 to 10 mg for 12 to 14 days every 1 to 2 months. Oral micronized progesterone may be administered at a dose of 100 mg daily or 200 mg for 12 to 14 days every 1 to 2 months. Likewise, progesterone suppositories may be administered at a dose of 50 mg daily or 100 mg for 12 to 14 days every 1 to 2 months.
- **Occasionally, individuals with mosaicism and gonadal streaks may ovulate and be able to conceive either spontaneously or after the institution of estrogen replacement therapy (52).**
- **If 17 α -hydroxylase deficiency is confirmed, treatment is instituted with corticosteroid replacement as well as estrogen.** Progestin is added if the patient has a uterus.

If possible, therapeutic measures are aimed at correcting the primary cause of amenorrhea:

- **Craniopharyngiomas may be resected with a transsphenoidal approach or during craniotomy,** depending on the size of the tumor. Some studies have shown improved prognosis with radiation therapy used in combination with limited tumor removal (36,53).
- **Germinomas are highly radiosensitive, and surgery is rarely indicated (54).**
- **Prolactinomas and hyperprolactinemia often may respond to dopamine agonists (*bromocriptine or cabergoline*) (55).**

- **Specific therapies are directed toward malnutrition, malabsorption, weight loss, anorexia nervosa, exercise amenorrhea, neoplasia, and chronic diseases..**
- **Logically, it would appear that patients with hypogonadotropic hypogonadism of hypothalamic origin should be treated with long-term administration of pulsatile GnRH. This form of therapy is often impractical,** however, because of the necessity to use an indwelling catheter and a portable pump for prolonged periods. Therefore, these patients should be treated with cyclic estrogen and progestin therapy at least until sexual maturity is achieved. Once sexual maturation is achieved, hormone replacement therapy can be continued to treat hypoestrogenic symptoms. Alternatively, consideration may be given to nonestrogenic regimens, such as bisphosphonates for maintenance of bone mass and prevention of osteoporosis.
- **Patients with Kallmann syndrome, as well as patients with exercise or stress amenorrhea and anorexia and weight loss, are treated with hormone replacement in a similar fashion as described for hypogonadotropic hypogonadism.**
- **If the patient has physiologic delay of puberty, the only management required is reassurance** that the anticipated development will occur eventually (56).

Individuals whose karyotypes contain a Y cell line (45,X/46,XY mosaicism, or pure gonadal dysgenesis 46,XY) are predisposed to gonadal ridge tumors, such as gonadoblastomas, dysgerminomas, and yolk sac tumors. The gonads of these individuals should be removed when the condition is diagnosed to prevent malignant transformation (34,50). There is some evidence that hirsute individuals without Y chromosomes should also undergo gonad removal. One patient with hirsutism and the karyotype 45,X was noted to have a streak gonad; the contralateral gonad was dysgenic and contained developing follicles, well-differentiated seminiferous tubules, and Leydig cells. This patient was found to be HY antigen-positive (57). Clomiphene citrate is ineffective in inducing ovulation in patients with hypogonadism who desire pregnancy because such patients are hypoestrogenic. In patients with hypogonadism, ovulation induction with injectable gonadotropins is generally successful, and pulsatile treatment with GnRH may be used in patients who have normal pituitary function. In patients without ovarian function, oocyte donation may be appropriate. **There have been recent reports of deaths in pregnant patients with Turner syndrome resulting from aortic dissection and rupture** (58). Careful counseling and investigation should be undertaken in patients with Turner syndrome before treating them with donated oocytes. Because most patients with hypogonadism and lack of sexual development are young, pregnancy is not desired.

Amenorrhea with Secondary Sexual Characteristics and Anatomic Abnormalities

Causes

Anatomic Abnormalities

Amenorrhea occurs if there is blockage of the outflow tract or if the outflow tract is missing (Table 27.2). An intact outflow tract includes a patent vagina as well as a functioning cervix and uterus. Any transverse blockage of the müllerian system (Buttram and Gibbons classification I) will cause amenorrhea (59). Such outflow obstructions include imperforate hymen, transverse vaginal septum, and hypoplasia or absence of

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the uterus, cervix, and vagina (Mayer–Rokitansky–Küster–Hauser syndrome).

Mayer–Rokitansky–Küster–Hauser syndrome has been associated with abnormal galactose metabolism (60). Of the patients with this syndrome, 15% have an absent, pelvic, or horseshoe kidney; 40% have a double urinary collecting system (61,62); and 5% to 12% have skeletal abnormalities (63). Transverse blockage of the outflow tract with an intact endometrium frequently causes cyclic pain without menstrual bleeding in adolescents. The blockage of blood flow can cause hematocolpos, hematometra, or hemoperitoneum. Endometriosis may develop.

Table 27.2 Anatomic Causes of Amenorrhea
<i>Secondary sexual characteristics present</i>
Müllerian anomalies
Imperforate hymen
Transverse vaginal septum
Mayer–Rokitansky–Küster–Hauser syndrome
Androgen insensitivity
True hermaphrodites
Absent endometrium
Asherman's syndrome
Secondary to prior uterine or cervical surgery
Curettage, especially postpartum
Cone biopsy
Loop electroexcision procedure
Secondary to infections
Pelvic inflammatory disease
IUD-related
Tuberculosis
Schistosomiasis
IUD, intrauterine device.

When the findings of the physical examination are normal, anatomic abnormalities may still be considered. A congenitally absent endometrium is a rare finding in patients with primary amenorrhea. Asherman syndrome, which is more common with secondary amenorrhea or hypomenorrhea, may occur in patients with risk factors for endometrial or cervical scarring. Such risk factors include a history of uterine or cervical surgery, infections related to use of an intrauterine device, and severe pelvic inflammatory disease. Asherman syndrome is found in 39% of patients undergoing hysterosalpingography who have previously undergone postpartum curettage (64). Infections such as tuberculosis and schistosomiasis may cause Asherman syndrome but are rare in the United States. Cervical stenosis resulting from surgical removal of dysplasia (cone biopsy, loop electroexcision procedure) may also lead to amenorrhea.

Androgen Insensitivity

Phenotypic females with complete congenital androgen insensitivity (previously called testicular feminization) develop secondary sexual characteristics but do not have menses. These patients are male pseudohermaphrodites. Genotypically, they are male (XY) but have a defect that prevents normal androgen receptor function, leading to the development of the female phenotype. Defects in the androgen receptor

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gene located on the X chromosome include absence of the gene that encodes for the androgen receptor and abnormalities in the binding domains of the receptor.

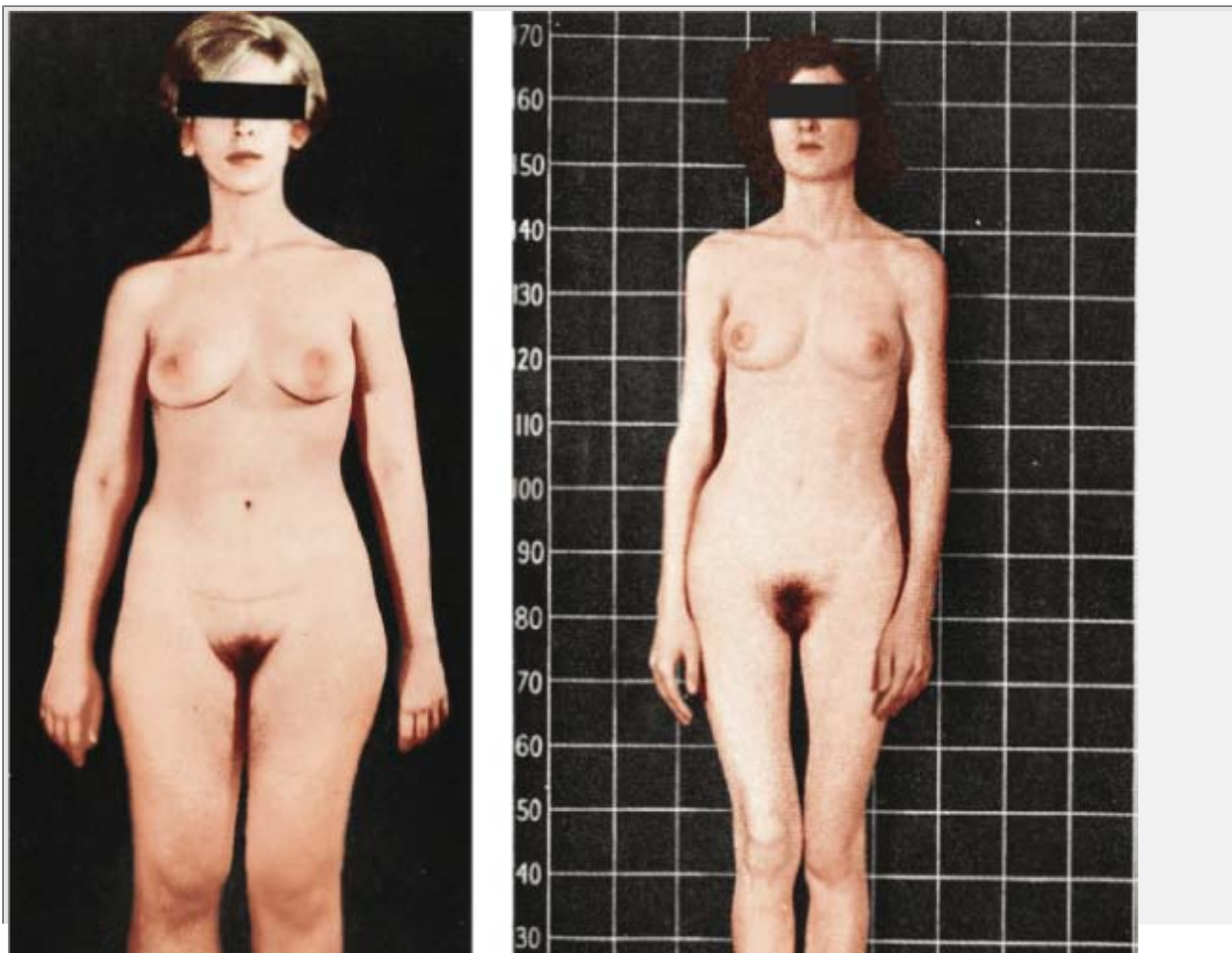
Androgen receptor deficits are diverse and may result from diminished receptor function or concentration. The diversity of androgen receptor mutations may be related to diversity in phenotype. More than 250 extremely diverse mutations have been described, with amino acid substitution being the far most common (65,66). Postreceptor defects also exist (67).

Total serum testosterone concentration is in the range of normal males. Because antimüllerian hormone is present and functions normally in these patients, internal female (müllerian) structures such as a uterus, vagina, and fallopian tubes are absent.

Testes rather than ovaries are present in the abdomen or in inguinal hernias because of the presence of normally functioning genes on the Y chromosome. Patients have a blind vaginal pouch and scant or absent axillary and pubic hair. These patients experience abundant breast development at puberty; however, the nipples are immature and the areolae are pale. Testosterone is not present during development to suppress the formation of breast tissues; at puberty, the conversion of testosterone to estrogen stimulates breast growth.

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Patients are unusually tall with eunuchoidal tendency (long arms with big hands and feet) (Fig. 27.2).



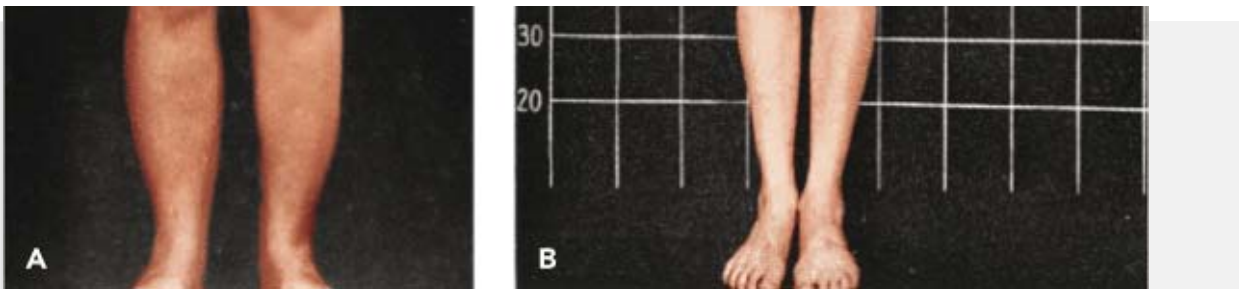


Figure 27.2 A: A well-developed patient with complete androgen insensitivity. Note the characteristic paucity of pubic hair and well-developed breasts. (From **Yen SSC, Jaffe RB.** *Reproductive endocrinology*. 3rd ed. Philadelphia, PA: WB Saunders, 1991:497, with permission.)
B: Another patient with androgen insensitivity syndrome with a contrasting thin body habitus. This is a 17-year-old twin 46,XY. (From **Jones HW Jr, Scott WW.** *Hermaphroditism, genital anomalies, and related endocrine disorders*. 2nd ed. Baltimore, MD: Williams & Wilkins, 1971, with permission.).

True Hermaphroditism

True hermaphroditism is a rare condition that should be considered as a possible cause of amenorrhea. Both male and female gonadal tissue are present in these patients, in whom XX, XY, and mosaic genotypes have been found. Two thirds of the patients menstruate, but menstruation has never been reported in XY genotypes. The external genitalia usually is ambiguous, and breast development frequently occurs in these individuals. **Fifteen percent of XX true hermaphrodites have SRY translocations, and another 10% have Y chromosomal mosaicism within the gonad (13).**

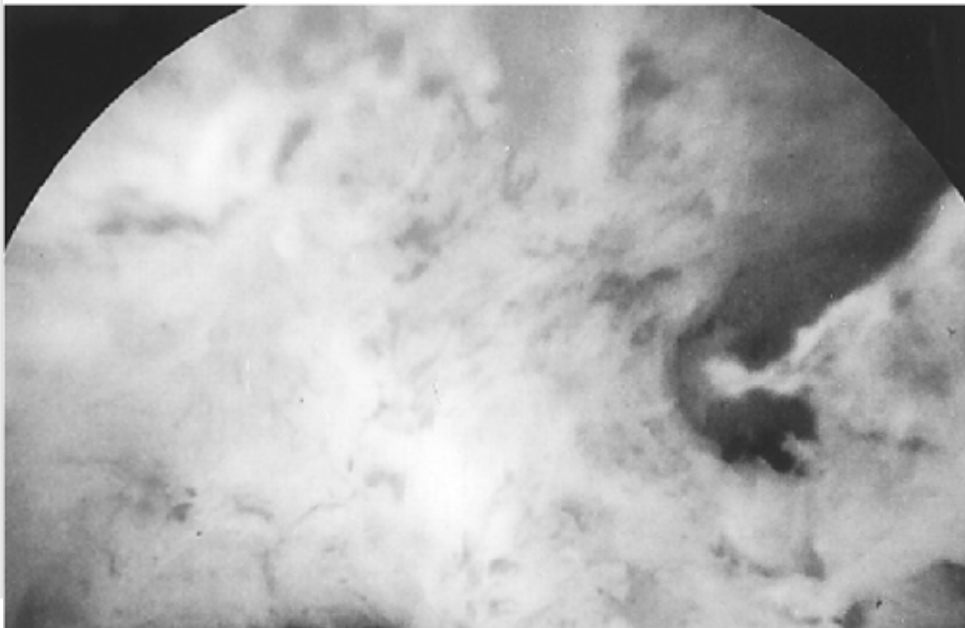
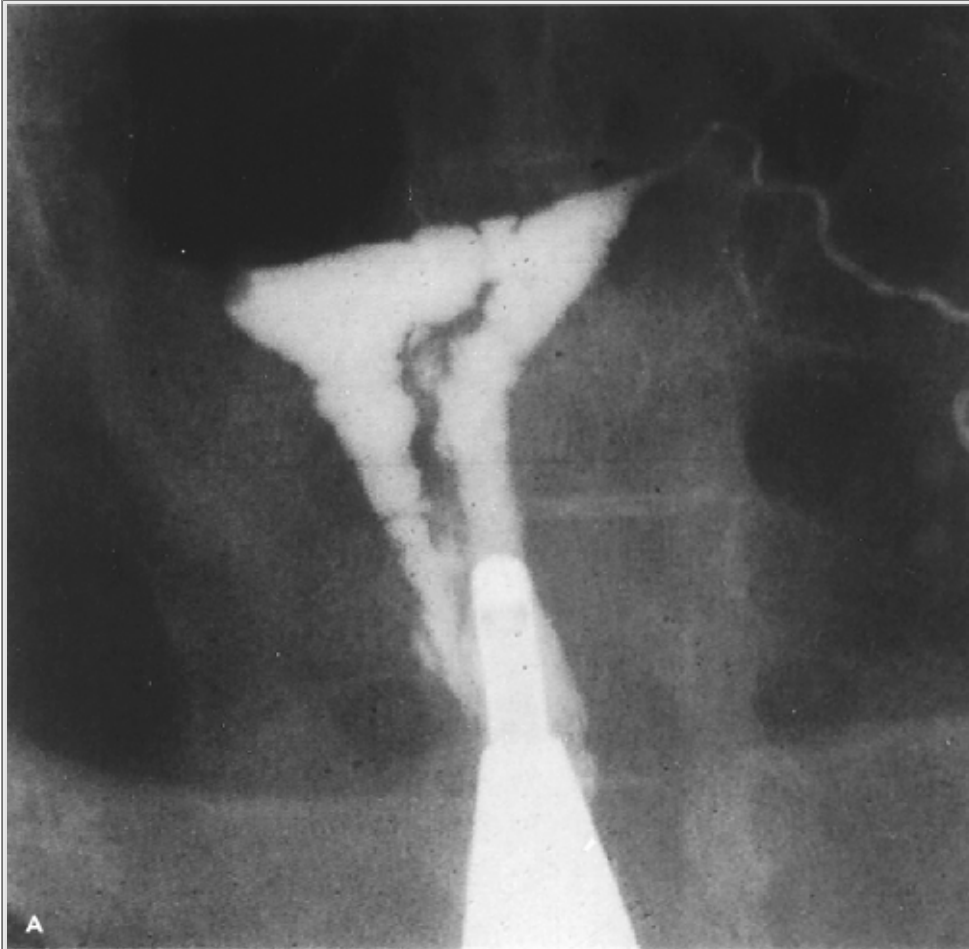
Diagnosis

Most congenital abnormalities can be diagnosed by physical examination:

- **An imperforate hymen is diagnosed by the presence of a bulging membrane that distends during Valsalva maneuver.** Ultrasonography or MRI is useful to identify the müllerian anomaly when the abnormality cannot be found by physical examination. The patient should also be examined for skeletal malformations and assessed with intravenous pyelography to detect concomitant renal abnormalities. These abnormalities occur less frequently than in müllerian agenesis (62).
- **It is difficult to differentiate a transverse septum or complete absence of the cervix and uterus in a female from a blind vaginal pouch in a male pseudohermaphrodite. Androgen insensitivity is diagnosed when pubic and axillary hair is absent.** To confirm the diagnosis, a karyotype determination should be performed to see whether a Y chromosome is present. In some patients, the defect in the androgen receptor is not complete, and virilization occurs.
- **An absent endometrium is an outflow tract abnormality that cannot be diagnosed by physical examination in a patient with primary amenorrhea.** This abnormality is so rare that in a patient with normal physical findings, it may be advisable to proceed with evaluation of endocrine abnormalities. Absence of the endometrium should be suspected in patients with primary amenorrhea and normal secondary sexual characteristics when the results of

hormonal studies are normal and the patients do not bleed after withdrawal of combined estrogen and progesterone replacement.

Asherman syndrome also cannot be diagnosed by physical examination. It is diagnosed by performing hysterosalpingography, saline infusion, ultrasonography, or hysteroscopy. These tests will show either complete obliteration or multiple filling defects caused by synechiae (Fig. 27.3). If tuberculosis or schistosomiasis is suspected, endometrial cultures should be performed.



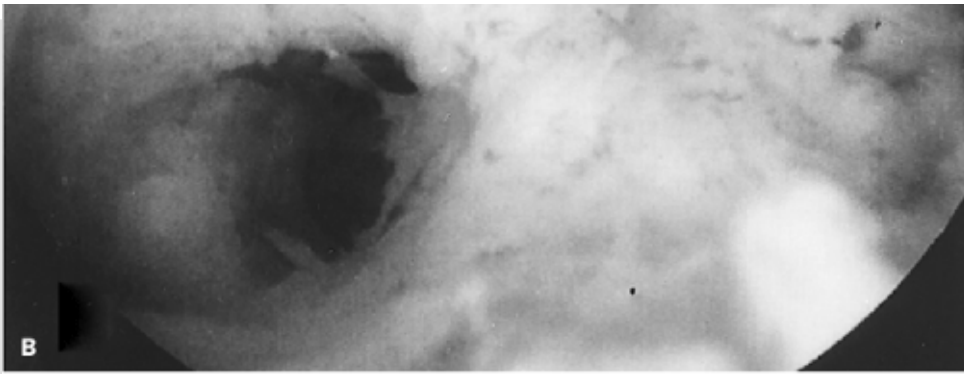


Figure 27.3 A: Intrauterine adhesion seen on hysterosalpingogram in a patient with Asherman syndrome. B: Hysteroscopic view of intrauterine adhesion in a patient with Asherman syndrome (From **Donnez J, Nisolle M.** *The encyclopedia of visual medicine series—an atlas of laser operative laparoscopy and hysteroscopy.* New York, NY: Parthenon Publishing Group, 1994: 306, with permission.).

Treatment

The treatment of congenital anomalies can be summarized as follows:.

- **Treatment of an imperforate hymen involves making a cruciate incision to open the vaginal orifice.** Most imperforate hymens are not diagnosed until a hematocolpos forms. It is unwise to place a needle into a hematocolpos without completely removing the obstruction because a pyocolpos may occur.
- **If a transverse septum is present, surgical removal is required.** Forty-six percent of transverse septa occur in the upper third of the vagina, and 40% occur

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in the middle third of the vagina (68). Frank dilators should be used to distend the vagina until it is healed to prevent vaginal adhesions (69). Patients have a fully functional reproductive system after surgery; however, patients with repaired high transverse septa have lower pregnancy rates (70).

- **Hypoplasia or absence of the cervix in the presence of a functioning uterus is more difficult to treat than other outflow obstructions.** Surgery to repair the cervix has not been successful, and hysterectomy is required (71). Endometriosis is a common finding, and it is questionable whether this condition should be treated initially with surgery or if it will resolve spontaneously after surgical repair of the obstruction. The ovaries should be retained to provide the benefits of estrogen and to allow for the possibility of future childbearing by removing mature oocytes for *in vitro* fertilization using a gestational carrier mother.
- **If the vagina is absent or short, progressive dilation is usually successful in making it functional** (69,72). If dilation fails or the patient is unable to perform dilation, the McIndoe split thickness graft technique may be performed (62,73,74). The initial use of vaginal dilators is required to maintain a functional vagina.

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In patients with complete androgen insensitivity, the testes should be removed after pubertal development is complete to prevent malignant degeneration (75). In patients with testes, 52% develop a neoplasia, most often a gonadoblastoma. Almost one half of the testicular neoplasms are malignant (dysgerminomas), but transformation usually does not occur until after puberty (76). In patients who develop virilization and have an XY karyotype, the testes should be removed immediately to preserve the female phenotype and to promote female gender identity. Bilateral laparoscopic gonadectomy is the preferred procedure for removal of intra-abdominal testes.

Adhesions in the cervix and uterus (Asherman syndrome) can be removed using hysteroscopic resection with scissors or electrocautery. A pediatric Foley catheter should be placed in the uterine cavity for 7 to 10 days postoperatively (along with systemic administration of broad-spectrum antibiotic therapy), and a 2-month course of high-dose estrogen therapy with monthly progesterone withdrawal is used to prevent reformation of adhesions. Eighty percent of patients thus treated achieve pregnancy, but complications including miscarriage, preterm labor, placenta previa, and placenta accreta are common (77). Cervical stenosis can be treated by cervical dilation.

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Amenorrhea with Secondary Sexual Characteristics and Nonanatomic Causes

Pregnancy must be considered in all women of reproductive age with amenorrhea.

Thyroid dysfunction and hyperprolactinemia also are frequent causes of amenorrhea and are discussed further in Chapter 28. Amenorrhea with secondary sexual characteristics and normal anatomy can be caused by ovarian failure, pituitary/hypothalamic lesions, and abnormal hypothalamic GnRH secretion.

Causes

Ovarian Failure

Ovarian failure is a normal occurrence during menopause. The age of menopause is determined by genetic inheritance. Once a patient is exposed to estrogen, estrogen withdrawal causes hot flashes and vaginal dryness. This occurs in approximately 50% of patients, whether ovarian failure is premature or occurs at the normal age (78). Physical examination reveals vaginal mucosal atrophy and no cervical mucus. **Ovarian failure occurs before 40 years of age in 1% to 5% of women and is considered pathologic (premature ovarian failure).** Early failure may be caused by decreased follicular endowment or accelerated follicular atresia. **If ovarian failure occurs before puberty, the patient's breasts will not develop (i.e., Turner syndrome), and gonadal agenesis results** (Tables 27.1 and 27.3).

Table 27.3 Causes of Ovarian Failure after Development of Secondary Sexual Characteristics

Chromosomal etiology.
Iatrogenic causes.
Radiation.
Chemotherapy.
Surgical alteration of ovarian blood supply.
Infections
Autoimmune disorders
Galactosemia (mild form or heterozygote)
Savage syndrome
Cigarette smoking
Idiopathic

Despite the array of causes of ovarian failure, in most cases the etiology cannot be determined. In some patients, ovarian failure resolves spontaneously. Pregnancies have been reported to occur after the diagnosis of ovarian failure in less than 0.09% to 8.2% of patients (78,79).

Cigarette smoking has been shown to have a clear inverse dose–response relationship with age of menopause (80). Other studies have confirmed this association, some eliminating potential confounding factors such as body weight, which could affect the age of menopause (81). Cigarette smoking alters both gametogenesis and hormonogenesis, suggesting an effect on the follicle. Smoking has also been shown to increase the risk of diminished ovarian reserve (82).

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Sex Chromosome Disorders

Deletion of the X chromosome (Turner syndrome) is associated with premature ovarian failure despite normal development of the ovaries because of accelerated atresia of the follicles (83). Mosaicism of an XO or XY cell line may cause ovarian failure in patients younger than 30 years of age. A deletion of a portion of the X chromosome may be present in patients with premature ovarian failure. The Xq21–28 region is critical (7,84). Several genes in this region have been identified as the cause of ovarian failure in humans. Examples include the *POF1B* gene located at Xq21 (85), the *DIAPH2* gene located at distal Xq21 (85), and the *XPNPEP2* gene located at Xq25 (86). The specific functions of these genes require further investigation. Undoubtedly, more genes that cause ovarian failure will be identified (87). In addition, a mutation of the *BMP15* gene located at Xp11.2 has been identified in two patients with premature ovarian failure (88). Mutations in the autosomal genes *FOXL2* and *ATM* have been shown to cause premature ovarian failure (13,89).

Individuals with a 47,XXX karyotype also may develop ovarian failure. Familial ovarian failure is inherited by dominant Mendelian inheritance in some cases (90).

Fragile X Carriers

Fragile X syndrome is the most common cause of inherited (X–linked) mental retardation. It is caused by inactivation of the *FMR1* gene located on Xq27.3 as a result of expansion of a CGG triplet repeat of more than 200 copies. The normal population has an average size repeat of 30. Female carriers of the disorder have between 60 to 200 repeats (premutations) and are not mentally retarded. These premutations are unstable and can expand in the next generation to transmit fragile X syndrome to male offspring, especially with individuals who have more than 100 repeats. Women who have premutations have a 15%

to 25% chance of premature ovarian failure (91,92). Interestingly, women with full mutations are not at higher risk for premature ovarian failure. It is hypothesized that expression of abnormal FMR1 mRNA produced by patients with the premutation causes dysfunction in the ovary, which does not occur when the *FMR1* gene is inactivated and not transcribed (91,92). **Patients with premature ovarian failure have a 4% to 5% chance of having the premutation for fragile X . If premature ovarian failure is present in another family member, the chance of finding a premutation increases to 15% (91,93).**

Iatrogenic Causes

Radiation, chemotherapy (especially alkylating agents such as cyclophosphamide) (94), surgical interference with ovarian blood supply, and infections can cause ovarian failure from early loss of follicles. A radiation dose of 800 cGy causes sterility in most individuals. Ovarian failure can be caused by as little as 150 cGy in some patients, especially if they are older than 40 years of age with limited follicle reserves.

In an evaluation of ovarian function in 100 childhood cancer survivors, 17 had premature ovarian failure. Those with spontaneous menses had smaller ovarian volume, fewer antral follicles, and lower inhibin B levels when compared with controls (95). Ovarian suppression with GnRH agonists and oral contraceptives to reduce the risk of ovarian failure have not been promising (96,97). Improvements in techniques of oocyte and ovarian tissue cryopreservation may allow future pregnancies in patients requiring treatments that cause follicular destruction (98,99).

Infections

In rare cases, mumps has been associated with premature ovarian failure (100). Tubo-ovarian abscess, even in the absence of surgical treatment, has also been associated with follicular destruction and premature ovarian failure (49). Cytomegalovirus has been shown postmortem to cause oophoritis, but premature ovarian failure had not developed yet clinically in the patient, so the relationship of cytomegalovirus to ovarian failure is unclear (101).

Autoimmune Disorders

Premature ovarian failure may be part of a polyglandular autoimmune syndrome. Antibodies are present in a variable number of patients with premature ovarian failure, depending on the autoimmune studies performed. One study showed that 92% of patients with premature ovarian failure had autoantibodies (102).

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However, only 20% of these patients exhibited signs of immunologic dysfunction, most frequently in the form of a thyroid disorder (79). Before treatment for thyroid deficiency, adrenal insufficiency characterized by hyperpigmentation, weakness, nausea, vomiting, diarrhea, and weight loss should be ruled out; otherwise, adrenal crisis may occur (12). Rarely, premature ovarian failure is associated with myasthenia gravis, idiopathic thrombocytopenia purpura, rheumatoid arthritis, vitiligo, autoimmune hemolytic anemia, diabetes mellitus, and other autoimmune disorders (103,104,105).

Galactosemia

Galactosemia is caused by a lack of functional galactose-1-phosphate uridylyl transferase. Galactose metabolites appear to have toxic effects on ovarian follicles, causing their premature destruction (106). Cataracts and mental retardation are also associated with galactosemia. There is also evidence that heterozygote carriers of this disorder may

Pituitary and hypothalamic

Craniopharyngioma

Germinoma

Tubercular granuloma

Sarcoid granuloma

Dermoid cyst

Pituitary

Nonfunctioning adenomas

Hormone-secreting adenomas

Prolactinoma

Cushing's disease

Acromegaly

Primary hyperthyroidism

Infarction

Lymphocytic hypophysitis

Surgical or radiologic ablations

Sheehan's syndrome

Diabetic vasculitis

Pituitary Lesions

Hypopituitarism is rare because a large portion of the gland must be destroyed before decreased hormonal secretion affects the patient clinically. The pituitary gland may be destroyed by tumors (nonfunctioning or hormone secreting), infarction, infiltrating lesions such as lymphocytic hypophysitis, granulomatous lesions, and surgical or radiologic ablations.

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Sheehan syndrome is associated with postpartum necrosis of the pituitary resulting from a hypotensive episode that, in its severe form (pituitary apoplexy), presents with the patient in shock. The patient may develop a localized, severe, retro-orbital headache or abnormalities in visual fields and visual acuity. Patients with a mild form of postpartum pituitary necrosis cannot lactate, lose pubic and axillary hair, and do not menstruate after delivery.

Diabetic vasculitis and sickle cell anemia rarely manifest as pituitary failure. Hypopituitarism is associated with hyposecretion of ACTH and thyroid-stimulating hormone (TSH) as well as gonadotropins; therefore, thyroid and adrenal function also must be evaluated.

If hypopituitarism occurs before puberty, menses and secondary sexual characteristics will not develop..

Growth hormone (GH), TSH, ACTH, and prolactin also are secreted by the pituitary, and the excess production of each by pituitary tumors causes menstrual abnormalities. **Excess prolactin secretion is one of the more common causes of amenorrhea (2).** The menstrual abnormalities are caused by adverse effects of these hormones on the GnRH pulse generator and not by direct effects on the ovary. Prolactinomas are the most common hormone-secreting tumors in the pituitary (see Chapter 28).

Altered Hypothalamic Gonadotropin-releasing Hormone Secretion

Abnormal secretion of GnRH accounts for one third of patients with amenorrhea

(110). Chronic disease, malnutrition, stress, psychiatric disorders, and exercise inhibit GnRH pulses, thus altering the menstrual cycle (Table 27.5). Other hormonal systems that produce excess or insufficient hormones can cause abnormal feedback and adversely affect GnRH secretion. In hyperprolactinemia, Cushing disease (excess ACTH), and acromegaly (excess GH), excess pituitary hormones are secreted that inhibit GnRH secretion. It is uncommon

to have functional hypothalamic amenorrhea without a secondary cause. Prognosis for recovery is better if the precipitating cause of the amenorrhea can be reversed (111).

Table 27.5 Abnormalities Affecting Release of Gonadotropin–Releasing Hormone

Variable estrogen status^a

Anorexia nervosa
Exercise–induced
Stress–induced
Pseudocyesis
Malnutrition
Chronic diseases
Diabetes mellitus
Renal disorders
Pulmonary disorders
Liver disease
Chronic infections
Addison's disease
Hyperprolactinemia
Thyroid dysfunction
<i>Euestrogenic states</i>
Obesity
Hyperandrogenism
Polycystic ovary syndrome
Cushing's syndrome
Congenital adrenal hyperplasia
Androgen–secreting adrenal tumors
Androgen–secreting ovarian tumors
Granulosa cell tumor
Idiopathic

^aSeverity of the condition determines estrogen status—the more severe, the more likely to manifest as hypoestrogenism.

When the decrease in GnRH pulsatility is severe, amenorrhea results. With less severe alterations in GnRH pulsatility, anovulation can occur. Even slight defects in the pulsatility may result in luteal phase defect.

The pulsatile secretion of GnRH is modulated by interactions with neurotransmitters and peripheral gonadal steroids. Endogenous opioids, corticotropin–releasing hormones (CRH), melatonin, and α -aminobutyric acid (GABA) inhibit the release of GnRH, whereas catecholamines, acetylcholine, and vasoactive intestinal peptide stimulate GnRH pulses. Dopamine and serotonin have variable effects (112).

Decreased leptin levels have been associated with hypothalamic amenorrhea

(113,114) regardless of whether it is caused by exercise, eating disorders, or idiopathic

factors. Leptin is a hormone secreted by adipocytes that is involved in energy hemostasis. Receptors are found in the hypothalamus and bone, making it an excellent candidate for a modulator of menstrual function and bone mass. Levels correlate with nutritional changes and body mass index. Administration of leptin to women with hypothalamic amenorrhea increases levels of LH, estradiol, insulinlike growth factor-1 (IGF-1), and thyroid hormone. Ovulation and increased bone mass also occurred in these patients (114).

Weight Loss and Dieting

Weight loss can cause amenorrhea even if weight doesn't decrease below normal. Loss of 10% body mass in 1 year is associated with amenorrhea. Some but not all of these women have an underlying eating disorder. Prognosis is good for the return of menses if the patients recover from the weight loss. Dieting without weight loss and changes in diet can also lead to amenorrhea (111).

Anorexia Nervosa

Anorexia nervosa is an eating disorder that affects 5% to 10% of adolescent women in the United States. The criteria for diagnosis of anorexia nervosa as stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) are refusal to maintain body weight above 15% below normal, an intense fear of becoming fat, altered perception of one's body image (ie, patients see themselves as fat despite being underweight), and amenorrhea. Patients attempt to maintain their low body weight by food restriction, induced vomiting, laxative abuse, and intense exercise. **This is a life-threatening disorder with a mortality rate as high as 9%.** Amenorrhea may precede, coincide, or follow the weight loss. Multiple hormonal patterns are altered. The 24-hour patterns of FSH and LH may show constantly low levels as seen in childhood or increased LH pulsatility during sleep consistent with the pattern seen in early puberty. Hypercortisolism is present despite normal ACTH levels, and the ACTH response to CRH administration is blunted. Circulating triiodothyronine (T₃) is low, yet circulating inactive reverse T₃ concentrations are high (115).

Patients may develop cold and heat intolerance, lanugo hair, hypotension, bradycardia, and diabetes insipidus. They may have yellowish discoloration of the skin resulting from elevated levels of serum carotene caused by altered vitamin A metabolism.

Patients with anorexia nervosa have combinations of restrictive and binge eating. Binge eating is associated with bulimia consisting of vomiting, laxative abuse, and diuretics to control weight. Signs of bulimia include tooth decay, parotid gland hypertrophy (chipmunk jowls), hypokalemia, and metabolic alkalosis (116).

Exercise

In patients with exercise-induced amenorrhea, there is a decrease in the frequency of GnRH pulses, which is assessed by measuring a decreased frequency of LH pulses. These patients are usually hypoestrogenic, but less severe alterations may cause minimal menstrual dysfunction (anovulation or luteal phase defect). The decrease in LH pulsatility can be caused by hormonal alterations, such as elevations in endogenous opioids, ACTH, prolactin, adrenal androgens, cortisol, and melatonin (117). Differences in body-fat content have been used to explain the different rates of amenorrhea by sport. Runners and

ballet dancers are at higher risk for amenorrhea than swimmers (118). It has been suggested that a minimum of 17% body fat is required for the initiation of menses and 22% body fat for the maintenance of menses (119). However, newer studies suggest that inappropriately low caloric intake during strenuous exercise is more important than body fat (120). **Higher-intensity training, poor nutrition, stress of competition, and associated eating disorders increase an athlete's risk for menstrual dysfunction (121). The "female athlete triad" consists of amenorrhea, osteoporosis, and eating disorders.**

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Osteoporosis may result in stress fractures during training and lifelong increased fracture risk. Stress fractures most commonly occur in the weight-bearing cortical bone such as the tibia, metatarsal, fibula, and femur. These athletes fail to reach peak bone mass and have abnormal bone mineralization. Scoliosis is also common (117).

Stress-induced Disorders

Stress-related amenorrhea can be caused by abnormalities in neuromodulation in hypothalamic GnRH secretion, similar to those that occur with exercise and anorexia nervosa. Excess endogenous opioids and elevations in CRH secretion inhibit the secretion of GnRH (112). These mechanisms are not fully understood but appear to be the common link between amenorrhea and chronic diseases, pseudocyesis, and malnutrition.

Obesity

Most obese patients have normal menstrual cycles, but the percentage of women with menstrual disorders increases from 2.6% in normal-weight patients to more than 8.4% in women above 75% ideal body weight. The menstrual disorder is more often irregular uterine bleeding with anovulation rather than amenorrhea. **Obese women have an excess number of fat cells in which extraglandular aromatization of androgen to estrogen occurs. They also have lower circulating levels of sex hormone-binding globulin, which allows a larger proportion of free androgens to be converted to estrone. Excess estrogen creates a higher risk for endometrial cancer for these women.** The decrease in sex hormone-binding globulin also allows an increase in free androgen levels, which initially are eliminated by an increased rate of metabolic clearance. This compensatory mechanism diminishes over time, and hirsutism can develop. Frequently, these patients are classified as having PCOS. Alterations in the secretion of endorphins, cortisol, insulin, growth hormone, and IGF-1 may interact with the abnormal estrogen and androgen feedback to the GnRH pulse generator to cause menstrual abnormalities.

Other Hormonal Factors

The secretion of hypothalamic neuromodulators can be altered by feedback from abnormal levels of peripheral hormones. Excesses or deficiencies of thyroid hormone, glucocorticoids, androgens, and estrogens can cause menstrual dysfunction. Even though **PCOS usually causes irregular bleeding rather than amenorrhea, it remains one of the most common causes of amenorrhea (2). It is likely that PCOS is the result of peripheral alteration in IGF-1, androgen, and estrogen levels, which leads to hypothalamic dysfunction** (see Chapter 28). Elevations in androgens (e.g., Sertoli-Leydig, hilus, and lipoid cell tumors) and estrogens (e.g., granulosa cell tumors) by ovarian tumors may lead to abnormal menstrual patterns, including amenorrhea. In patients who are hirsute and amenorrheic, androgen-secreting adrenal tumors and congenital adrenal hyperplasia should be considered.

Excess secretion of GH, TSH, ACTH, and prolactin from the pituitary gland can cause abnormal feedback inhibition of GnRH secretion, leading to amenorrhea.

Growth hormone excess causes acromegaly, which may be associated with anovulation, hirsutism, and polycystic ovaries as a result of stimulation of the ovary by IGF-1. More commonly, GH excess is accompanied by amenorrhea, low gonadotropin levels, and elevated prolactin levels. Acromegaly is recognized by enlargement of facial features, hands, and feet; hyperhidrosis; visceral organ enlargement; and multiple skin tags. Cushing disease is caused by an ACTH-secreting pituitary tumor, which is manifested by truncal obesity, moon facies, hirsutism, proximal weakness, depression, and menstrual dysfunction.

Diagnosis

A pregnancy test (urine or serum hCG) should be performed in a reproductive-age woman who has amenorrhea with normal secondary sexual characteristics and a normal pelvic examination. If the results of the pregnancy test are negative, the evaluation of amenorrhea is as follows:

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- **Serum TSH.**
- **Serum prolactin.**
- **FSH levels.**
- **Estrogen status.**
- **Imaging of the pituitary and hypothalamic assessment as necessary.**

Thyroid-stimulating Hormone and Prolactin Levels

Consideration should be given to thyroid disorders and hyperprolactinemia in women with amenorrhea due to the relatively common incidence of these conditions..

- **Sensitive TSH assays can be used to evaluate hypothyroidism and hyperthyroidism.** Further evaluation of a thyroid disorder is required if abnormalities in TSH levels are found.
- **Hyperprolactinemia is a common cause of anovulation in women. If elevated TSH and prolactin levels are found, the hypothyroidism should be treated before hyperprolactinemia is treated.** Often, the prolactin level will normalize with treatment of hypothyroidism because thyroid-releasing hormone, which is elevated in hypothyroidism, stimulates prolactin secretion.
- **Magnetic resonance imaging should be performed for persistently elevated prolactin levels..**

Follicle-stimulating Hormone Levels

Assessment of serum FSH levels is required to determine whether the patient has hypergonadotropic, hypogonadotropic, or eugonadotropic amenorrhea. **A circulating FSH level of greater than 25 to 40 mIU/mL indicated on at least two blood samples is indicative of hypergonadotropic amenorrhea.** Hypergonadotropism signifies that the cause of amenorrhea is at the level of the ovary. The history should establish whether the cause of ovarian failure is chemotherapy or radiation therapy. A galactose-1 phosphate uridyl transferase level should be measured to assess the patient for galactosemia or carrier status. Fragile X carrier status should be evaluated in patients with first-degree relatives with premature ovarian failure.

In patients younger than 30 years of age with hypergonadotropic amenorrhea, a karyotype is required to rule out the presence of a Y cell line. *In situ* hybridization studies may prove the existence of Y chromosomal material with a Y-specific probe when the karyotype is normal (122). It is important to identify Y chromosomal material so it may be removed to prevent malignant degeneration.

There is much debate regarding the extent of an autoimmune workup required for a patient with ovarian failure: .

- It is reasonable to screen patients with nonspecific tests such as those to detect antinuclear antibodies, rheumatoid factor, and erythrocytic sedimentation rate.
 - A normal partial thromboplastin time is sufficient to exclude lupus anticoagulant.
 - Assessments of serum electrolytes, calcium, and phosphorus concentrations can be used to evaluate the possibility that parathyroid autoantibodies are active.
-
- Other assessments that should be performed include TSH, antithyroglobulin antibodies, antimicrosomal antibodies to evaluate thyroid status, and 24-hour urinary free cortisol to detect the presence of antiadrenal antibodies.
 - A more extensive workup may include parietal cell antibodies, islets of Langerhans antibodies, and antiadrenal antibodies; it is unclear, however, if the results of these tests will alter clinical management.

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Tests should be repeated yearly because of the transient nature of autoimmune disorders.

In a patient with hypergonadotropic amenorrhea, ovarian biopsy to determine whether follicles are present is not advised. Even if oocytes are found, there is no good method of stimulating those oocytes to ovulate. Some patients with negative biopsy results later ovulate spontaneously. This can be explained by considering that the biopsies sample only a small portion of the ovary (79).

Assessment of Estrogen Status

Traditionally, estrogen status has been determined by giving medroxyprogesterone acetate, either 5 mg or 10 mg, for 10 days. Withdrawal bleeding usually occurs within 2 to 10 days after the last dose. There is a debate as to how much bleeding constitutes withdrawal bleeding. There is a 20% false-positive rate in women who do not bleed despite having estrogen, and a 40% false-negative rate in women who bleed despite low estrogen states caused by hypothalamic dysfunction. A 50% false-negative rate occurs with ovarian failure (2). If vaginal bleeding does not occur after oral administration of progesterone, frequently 100 to 200 mg progesterone in oil is given intramuscularly. Other ways of testing for estrogen status may be quicker and easier. The development of vaginal dryness and hot flashes increase the likelihood of a diagnosis of hypoestrogenism. A sample of vaginal secretions can be obtained during the physical examination, and mucosal estrogen response can be demonstrated by the presence of superficial cells. A serum estradiol level higher than 40 pg/mL is considered adequate, but interassay discrepancies often exist. A DEXA (dual-energy x-ray absorptiometry) scan to determine bone mineral density should be performed in any patient in whom hypoestrogenism is suspected.

The finding of vaginal bleeding after progesterone challenge is important when Asherman syndrome is suspected. In a patient with primary amenorrhea and an apparently normal estrogen status, a progesterone challenge will diagnose the rare finding of congenitally absent endometrium. If estrogen status is questioned, 2.5 mg *conjugated estrogen* or 2 mg *micronized estradiol* can be given for 25 days with 5 to 10 mg of *medroxyprogesterone acetate* added for the last 10 days. Congenital absence of the endometrium is confirmed if no bleeding occurs with this regimen in a patient with primary amenorrhea and no physical abnormalities. Transvaginal ultrasound to assess endometrial thickness may also be helpful. If similar findings occur in patients with secondary amenorrhea, Asherman syndrome is diagnosed. **Asherman syndrome must be confirmed by showing filling defects on hysterosalpingography or by visualizing adhesions with hysteroscopy.**

Assessment of the Pituitary and Hypothalamus

If the patient is hypoestrogenic and the FSH level is not high, pituitary and hypothalamic lesions should be excluded.

- **A complete neurologic examination**, including electroencephalography, may help localize a lesion.
 - **Either CT or MRI scanning should be performed** to confirm the presence of a tumor. MRI will identify smaller lesions than CT; if a lesion is too small for identification by CT, it may be clinically insignificant.
-
- **After anatomic lesions have been excluded, the patient's history** of weight changes, exercise, eating habits, body image, and career or school achievements are important factors in differentiating anorexia nervosa, malnutrition, obesity, or exercise-induced or stress-induced menstrual disorders.

Amenorrheic patients who have hypothalamic dysfunction and are hypoestrogenic may have disorders similar to those who have normal estrogen levels. **The hypothalamic**

dysfunction caused by chronic disease, anorexia nervosa, stress, and malnutrition may be more severe or may exist for a more prolonged time in hypoestrogenic patients than in euestrogenic patients..

Patients with appropriate clinical findings should undergo screening for other hormonal alterations: .

- **Androgen levels should be assessed** in any hirsute patient to ensure that adrenal and ovarian tumors are not present as well as to diagnose PCOS (see Chapter 28).
- **Acromegaly** is suggested by coarse facial features, large doughy hands, and hyperhidrosis and **may be confirmed by measuring IGF-1 levels..**
- In patients with truncal obesity, hirsutism, hypertension, and erythematous striae, **Cushing syndrome should be ruled out** by assessing 24-hour urinary cortisol levels or performing a 1-mg overnight dexamethasone suppression test.

Treatment

The treatment of nonanatomic causes of amenorrhea associated with secondary sexual characteristics varies widely according to the cause. The underlying disorder should be treated whenever possible. Patients who are pregnant may be counseled regarding the options for continued care. When thyroid abnormalities are detected, thyroid hormone, radioactive iodine, or antithyroid drugs may be administered as appropriate. When hyperprolactinemia is present, treatment may include discontinuation of contributing medications, treatment with dopamine agonists such as *bromocriptine* or *cabergoline*, and, rarely, surgery for particularly large pituitary tumors. When ovarian failure causes amenorrhea, hormone replacement may be considered to diminish menopausal symptoms as well as to prevent osteoporosis. Counseling regarding the risks and benefits of hormone replacement therapy is indicated (123). Gonadectomy is required when a Y cell line is present.

Surgical removal, radiation therapy, or a combination of both is generally advocated for treatment of central nervous system tumors other than prolactinomas. It may be necessary to treat individuals who have panhypopituitarism with various replacement regimens once all the deficits have been elucidated. These regimens include estrogen replacement for lack of gonadotropins, corticosteroid replacement for lack of ACTH, thyroid hormone for lack of TSH, and *desmopressin acetate (1-deamino-8-D-AVP [DDAVP])* to replace vasopressin.

The treatment of amenorrhea associated with hypothalamic dysfunction also depends on the underlying cause: .

- **Hormonally active ovarian tumors are surgically removed..**
- **Obesity, malnutrition or chronic disease, Cushing syndrome, and acromegaly should be specifically treated.**

Pseudocyesis and stress-induced amenorrhea may respond to psychotherapy..

Exercise-induced amenorrhea may improve with moderation of activity and weight gain, when appropriate. If hypoestrogenism persists, higher doses of estrogen may be needed in these women than in older menopausal women to maintain bone density. In addition, 1,200 to 1,500 mg of calcium and 400 IU of vitamin D daily is advised. Bisphosphonates do not improve bone density in amenorrheic athletes because it is lack of bone formation rather than increased resorption that causes the osteopenia. In addition, the use of bisphosphonates is not advised because they can be deposited into the bone, and long-term effects, especially during pregnancy, are unknown (117).

Treatment of anorexia nervosa generally demands a multidisciplinary approach, with severe cases requiring hospitalization..

Chronic anovulation or PCOS may be treated after identifying the desires of the patient. Patients often are concerned about their lack of menstruation but not about hirsutism or infertility. **The endometrium of these individuals should be protected from the environment of unopposed estrogen** that accompanies the anovulatory state. Oral contraceptives are a good alternative for those patients who also require contraception. For those patients who are not candidates for oral contraceptive use, cyclic administration of progestin is advised. This treatment option presumes an adequate estrogenic environment to induce proliferation of the endometrium and is not sufficient to cause withdrawal bleeding in patients who are hypoestrogenic (i.e., those who have anorexia nervosa). **In these individuals, estrogen replacement must be added to the progestin regimen for successful menstrual regulation and prevention of osteoporosis. The most common progestin used to induce withdrawal bleeding and thus protect the endometrium from hyperplastic transformation is medroxyprogesterone acetate** (10 mg for 10 days per month). Occasionally, ovulation may occur; therefore, patients should be made aware that pregnancy is possible and appropriate contraceptive measures should be used. There is concern that *medroxyprogesterone acetate* used in early pregnancy may increase the incidence of pseudohermaphroditism (124). Alternatively, *progesterone* suppositories (50–100 mg) or *micronized progesterone* (200 mg) could be given for 10 days to induce withdrawal bleeding. No increased incidence of birth defects has been associated with the use of these natural progesterones (125).

When chronic anovulation is caused by attenuated congenital adrenal hyperplasia, glucocorticoid administration (i.e., dexamethasone 0.5 mg at bedtime) is sometimes successful in restoring the normal feedback mechanisms, thereby permitting regular menstruation and ovulation.

Hirsutism

Patients who have oligomenorrhea or amenorrhea resulting from chronic anovulation may have hirsutism (Chapter 28). **After ruling out androgen-secreting tumors and congenital adrenal hyperplasia, treatment may be aimed at decreasing coarse hair growth.**

Oral Contraceptives

Oral contraceptives may be effective by decreasing ovarian androgen production as well as increasing circulating levels of sex hormone-binding globulin, leading to decreased free androgen circulation.

Antiandrogens

Spirolactone decreases androgen production and competes with androgens at the androgen receptor level. Side effects include limited diuresis and dysfunctional uterine bleeding.

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Flutamide is approved by the U.S. Food and Drug Administration (FDA) for adjuvant therapy in prostatic cancer and for treatment of hirsutism. Its effects are similar to those of *spironolactone* with fewer side effects (126). Liver function should be monitored because of the rare complication of hepatotoxicity.

Cyproterone acetate, a strong progestin and antiandrogen, is used widely abroad but is not currently available in the United States. It is usually administered in combination with *ethinyl estradiol* in an oral contraceptive. By decreasing circulating androgen and LH levels, and by inducing antagonism of androgen effects at the peripheral level, *cyproterone acetate* is effective in treating hirsutism (127).

GnRH Agonist

GnRH agonist administration with add-back therapy is increasingly being used in the United States. Administration of GnRH agonist agents virtually eliminates ovarian steroid production, and estrogen-progestin add-back therapy allows long-term administration and protection against osteoporosis.

5 α -Reductase Inhibitors

Finasteride, a 5 α -reductase inhibitor, is approved by the FDA for the treatment of benign prostatic hypertrophy (*Proscar*) and male pattern baldness (*Propecia*). It is effective in treating hirsutism, although perhaps no more effective than other available agents (128,129). *Finasteride* has significant teratogenic potential, which precludes its use in any woman who may become pregnant. Its major advantage is that it is exceptionally well tolerated and may be used when side effects preclude the use of other therapeutic options for hirsutism.

Eflornithine hydrochloride, a topical cream, has been approved by the FDA for use on the face and chin. Improvements in facial hirsutism may be seen in 4 to 8 weeks of twice-daily applications.

Ovulation Induction

A large subset of patients with amenorrhea or oligomenorrhea and chronic anovulation seek care because they are unable to conceive (Chapter 30). Ovulation induction therapy is generally the treatment of choice for such patients, but pretreatment counseling should be provided in sufficient detail to ensure realistic expectations. The patient should be provided with information regarding the chances of a successful pregnancy (considering age of the patient and treatment modality), potential complications (hyperstimulation and multiple gestation), expense, time, and psychological impact involved in completing the course of therapy (130). **Patients may be advised that there is no increase in congenital anomalies in children born following ovulation induction** (131).

Earlier studies have raised the possibility of a relationship between ovulation induction and the risk of ovarian cancer (132,133). Ongoing studies are attempting to address this issue

conclusively, but **data support an increase of approximately 2.5-fold in ovarian cancer in patients with infertility, which appears unrelated to the use of ovulation-inducing drugs** (134,135). **There is no conclusive evidence to date to link fertility drug use and ovarian cancer** (136); thus, no change in current ovulation induction practices seems warranted at present. **Pregnancy and treatment with oral contraceptives before or after childbearing may protect against ovarian cancer.**

Clomiphene citrate is the usual first choice for ovulation induction in most patients because of its relative safety, efficacy, route of administration (oral), and relatively low cost (137). *Clomiphene citrate* is indicated primarily in patients with adequate levels of estrogen and normal levels of FSH and prolactin. It is generally ineffective in hypogonadotropic patients who already have a poor estrogen supply (138). Patients with inappropriate gonadotropin release (an increased LH-to-FSH ratio), such as that which occurs in PCOS, are also candidates for therapy with *clomiphene citrate*. **As many as 80% of**

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certain patients can be expected to ovulate after clomiphene citrate therapy, and pregnancy rates approach 40% (130). Contraindications to the use of *clomiphene citrate* include pregnancy, liver disease, and pre-existing ovarian cysts. Side effects include hot flashes (>11% of patients) and poorly understood visual symptoms, which generally have been viewed as an indication to discontinue subsequent *clomiphene citrate* use. The incidence of multiple gestation ranges from 6.25% to 12.3% (130). The most commonly recommended treatment regimen is 50 mg daily for 5 days, beginning on the third to fifth day of menstrual or withdrawal bleeding. Cycles are easily monitored by measuring midluteal progesterone levels to assess ovulation. Measurement of midcycle estradiol levels and ultrasonographic monitoring to assess folliculogenesis may also be helpful, especially when hCG is used to induce ovulation. Endometrial thinning caused by the antiestrogenic effects of *clomiphene citrate* may also be detected with midcycle ultrasound. With these data, it is possible to immediately adjust the dose in the subsequent cycle if a given regimen is ineffective. Dosage increases of 50 mg/day are usually used, and more than 70% of conceptions occur at doses no higher than 100 mg/day for 5 days (139). Dosages higher than 150 mg/day for 5 days are usually ineffective, and patients who remain anovulatory with this dosage should undergo further evaluation accompanied by changes in the therapeutic plan. Longer courses of *clomiphene citrate* therapy, as well as adjunctive therapy with glucocorticoids and hCG, have been recommended (138). **Patients with PCOS, especially those with insulin resistance, may benefit from the use of insulin-sensitizing agents**, used either as primary or adjunctive therapy (140). These agents include the biguanide *metformin* and thiazolidinediones (*rosiglitazone* and *pioglitazone*). Thinning of the endometrium at midcycle in the face of adequate midcycle estradiol and midluteal progesterone levels is generally an indication to change therapy to injectable gonadotropins.

Women who do not ovulate or become pregnant with *clomiphene citrate*, as well as women with hypogonadotropic hypoestrogenic anovulation, may be candidates for therapy with injectable gonadotropins. Much higher pregnancy rates (up to 90%) occur in the latter category. Available preparations include recombinant FSH or products purified from the urine of menopausal women (FSH or FSH-LH combinations). Oral gonadotropin therapy is undergoing research and development. Administration protocols and dosages vary widely and should be adjusted to individual needs. Safe administration requires careful monitoring of ovarian response with ultrasonography and serial estradiol measurements. In general, gonadotropins are administered at a dose of 50 to 150 IU/day by subcutaneous or intramuscular injection for 3 to 5 days, after which time estradiol and follicular monitoring commence. In most cycles, gonadotropin is administered 7 to 12 days. Ovulation is triggered by subcutaneous or intramuscular injection of 5,000 to 10,000 IU hCG or

subcutaneous injection of 250 µg of recombinant hCG once the lead follicle reaches 16 to 20 mm in diameter based on ultrasonographic assessments. Ovulation generally occurs approximately 36 hours after hCG administration. Luteal phase support is sometimes provided with the administration of progesterone supplementation or with additional injections of hCG.

The two major complications associated with induction of ovulation with gonadotropins are multiple pregnancy (10%–30%) and ovarian hyperstimulation syndrome.

The incidence of both of these complications can be lowered by careful monitoring. Cycles complicated by the recruitment of numerous follicles or by estradiol levels approaching or exceeding 2,000 pg/mL may be canceled by withholding the ovulatory dose of hCG. Selected patients may be converted safely to *in vitro* fertilization. Because severe ovarian hyperstimulation syndrome is life-threatening and may lead to prolonged hospitalization, ovulation induction with gonadotropins generally is performed by experienced practitioners who devote a significant portion of their practice to the treatment of infertility.

Ovulation induction with GnRH may be effective in patients who have chronic anovulation associated with low levels of estrogen and gonadotropins. For therapy to

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be successful, a functional ovary and pituitary gland must be present. Therefore, patients with ovarian or pituitary failure do not respond to GnRH therapy. To be effective, GnRH must be administered in a pulsatile fashion, either intravenously or subcutaneously by a programmable pump. Ovulation induction with GnRH, as compared with gonadotropins, is associated with a relatively low incidence of ovarian hyperstimulation and multiple births. In addition, the need for appropriate timing of the ovulatory dose of hCG is avoided because patients treated with pulsatile GnRH have an appropriately timed endogenous LH surge. Disadvantages are mainly related to maintaining the programmable pump and injection site. After ovulation, luteal phase support is necessary and may be provided with hCG, progesterone, or continuation of the GnRH therapy.

Patients who lack oocytes (ovarian failure) and desire pregnancy may be candidates for oocyte donation.

Oocytes may be harvested after ovulation induction from appropriate donors, fertilized with sperm from the recipient's husband, and transferred into the recipient's uterus after the endometrium has been appropriately prepared with hormonal regimens. Estrogen and progesterone are used to prepare the endometrium for implantation of the transferred embryo(s).

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Endocrine Disorders

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- **Hyperandrogenism most often presents as hirsutism, which usually arises as a result of androgen excess related to abnormalities of function in the ovary or adrenal glands. By contrast, virilization is rare and indicates marked elevations in androgen levels..**
- **The most common cause of hyperandrogenism and hirsutism is polycystic ovarian syndrome (PCOS). There are only two major criteria for the diagnosis of PCOS: anovulation and the presence of hyperandrogenism as established by clinical or laboratory means. Patients with PCOS frequently exhibit insulin resistance and hyperinsulinemia..**
- **Combination oral contraceptives (OCs) decrease adrenal and ovarian androgen production and reduce hair growth in nearly two thirds of hirsute patients..**
- **Because hyperinsulinemia appears to play a role in PCOS-associated**

anovulation, treatment with insulin sensitizers may shift the endocrine balance toward ovulation and pregnancy, either alone or in combination with other treatment modalities..

- Excluding cases that are of iatrogenic or factitious etiology, adrenocorticotrophic hormone (ACTH)–independent forms of *Cushing syndrome* are adrenal in origin. Adrenal cancers are usually very large by the time Cushing syndrome is manifest..

- *Congenital adrenal hyperplasia* is transmitted as an autosomal recessive disorder. Deficiency of 21–hydroxylase is responsible for more than 90% of cases of adrenal hyperplasia resulting from adrenal synthetic enzyme deficiency..

- Patients with severe hirsutism, virilization, or recent and rapidly progressing signs of androgen excess require careful investigation for the presence of an androgen–secreting neoplasm. Ovarian neoplasms are the most frequent androgen–producing tumors..

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- Elevations in prolactin may cause amenorrhea or galactorrhea. Amenorrhea without galactorrhea is associated with hyperprolactinemia in approximately 15% of women. In patients with both galactorrhea and amenorrhea, approximately two thirds will have hyperprolactinemia; of those, approximately one third will have a pituitary adenoma. In more than one third of women with hyperprolactinemia, a radiologic abnormality consistent with a microadenoma (> 1 cm) is found..

- Because levels of thyroid–stimulating hormone (TSH) are sensitive to excessive or deficient levels of circulating thyroid hormone, and because most disorders of hyperthyroidism and hypothyroidism are related to dysfunction of the thyroid gland, TSH levels are used to screen for these disorders. The most common thyroid abnormalities in women, autoimmune thyroid disorders, represent the combined effects of the multiple antibodies produced. Severe primary hypothyroidism is associated with amenorrhea or anovulation. The classic triad of exophthalmos, goiter, and hyperthyroidism in *Graves disease* is associated with symptoms of hyperthyroidism..

The endocrine disorders encountered most frequently in gynecologic patients are those related to disturbances in the regular occurrence of ovulation and accompanying menstruation. **The most prevalent problems are those characterized by androgen excess, often with insulin resistance, including what is arguably the most common endocrinopathy in women—polycystic ovary syndrome (PCOS).** Other conditions leading to ovulatory dysfunction, hirsutism, or virilization, as well as common disorders of the pituitary and thyroid glands associated with reproductive abnormalities, are reviewed in this chapter.

Hyperandrogenism

Hyperandrogenism most often presents as hirsutism, which usually arises as a result of androgen excess related to abnormalities of function in the ovary or adrenal glands, constitutive increase in expression of androgen effects at the level of the pilosebaceous unit, or a combination of the two. **By contrast, virilization is rare and indicates marked elevations in androgen levels.** Virilization usually is caused by an ovarian or adrenal neoplasm, which may be benign or malignant.

Hirsutism

The most frequent manifestation of androgen excess in women, hirsutism is defined as excessive growth of terminal hair in a male distribution. This condition refers particularly to midline hair, sideburns, moustache, beard, chest or intermammary hair, and inner thigh and midline lower back hair entering the intergluteal area. The response of the pilosebaceous unit to androgens in these androgen-responsive areas transforms vellus hair (fine, nonpigmented, short) that is normally present into terminal hair (coarse, stiff, pigmented, and long).

Androgen effects on hair vary in relation to specific regions of the body surface. Hair that shows no androgen dependence includes lanugo, eyebrows, and eyelashes. The hair of the limbs and portions of the trunk exhibits minimal sensitivity to androgens. Pilosebaceous units of the axilla and pubic region are sensitive to low levels of androgens. Even the modest androgenic effects of adult levels of androgens of adrenal origin are sufficient for substantial expression of terminal hair in these areas. Follicles in the distribution associated with male patterns of facial and body hair (midline, facial, inframammary) require higher levels of androgens, such as those seen with normal testicular function or abnormal

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ovarian or adrenal androgen production. Scalp hair is inhibited by gonadal androgens in varying degrees, as determined by age and genetic determination of follicular responsiveness, resulting in the common frontal–parietal balding seen in some men and in virilized women. **Hirsutism results from both increased androgen production and skin sensitivity to androgens. Skin sensitivity depends on the genetically determined local activity of 5 α -reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT), the bioactive androgen in hair follicles.**

Hair demonstrates cyclic activity between growth (*anagen*), involution (*catagen*), and resting (*telogen*) phases. The durations of both the growth and resting phases vary according to region of the body, genetic factors, age, and hormonal effects. The cycles of growth, rest, and shedding are normally dyssynchronous, but when synchronous entry into telogen phase is triggered by major metabolic or endocrine events such as pregnancy and delivery or severe illness, dramatic (although transient) hair loss may occur in the following months (*telogen effluvium*).

Hirsutism is a relative, rather than absolute, designation. What is normal in one setting may be considered abnormal in others; social and clinical reactions to hirsutism may vary significantly, reflecting ethnic variation in skin sensitivity to androgens and cultural ideals. Androgen-dependent hair (excluding pubic and axillary hair) occurs in only 5% of premenopausal Caucasian women and is considered abnormal by white women of North America, whereas considerable facial and male pattern hair in other parts of the body may be more common and acceptable among groups such as Inuit women and women of Mediterranean background.

Hypertrichosis and Virilization

Two conditions should be distinguished from hirsutism. **Hypertrichosis is the term reserved for the presence of androgen-independent terminal hair in nonsexual areas, such as the trunk and extremities.** This condition may result from an autosomal-dominant congenital disorder, a metabolic disorder (such as anorexia nervosa, hyperthyroidism, porphyria cutanea tarda), or medication use (e.g., acetazolamide, corticosteroids, cyclosporine, diazoxide, interferon, minoxidil, phenytoin, streptomycin). **Virilization is a marked and global masculine transformation that includes coarsening of the voice, increase in muscle mass, clitoromegaly (normal clitoral dimensions plus or minus standard deviation are 3.4 + 1 mm width by 5.1 + 1.4 mm length), and features of defeminization (loss of breast volume and body fat contributing to feminine body contour)** (1). Although hirsutism accompanies virilization, the presence of virilization indicates a high likelihood of a more serious condition than those that occur with hirsutism alone. The history should focus on the age at onset and rate of progression of hirsutism or virilization. **A rapid rate of progression of androgen effects or the presence of virilization, regardless whether it occurs before, during, or after puberty, is associated with a more severe degree of hyperandrogenism and should raise suspicion of ovarian and adrenal neoplasms or Cushing syndrome.** Anovulation, manifesting as amenorrhea or oligomenorrhea, increases the probability of underlying hyperandrogenism. Hirsutism occurring with regular cycles is more often associated with normal androgen levels; it is attributed to increased genetic sensitivity of the pilosebaceous unit and is termed *idiopathic hirsutism*. Anovulation virtually always occurs in the presence of virilization.

Determining the extent of hirsutism requires a sensitive and tactful approach by the physician and should include questions about shaving and the use of chemical or mechanical depilatories. Typically, clinical evaluation of the degree of hirsutism is subjectively classified as mild, moderate, or severe. Objective assessment is helpful, however, especially in establishing a baseline from which therapy can be evaluated. A hirsutism scoring scale of androgen-sensitive hair in nine body areas rated on a scale of 0 to 4 has been used (2). Hirsutism is defined as a score higher than 8.

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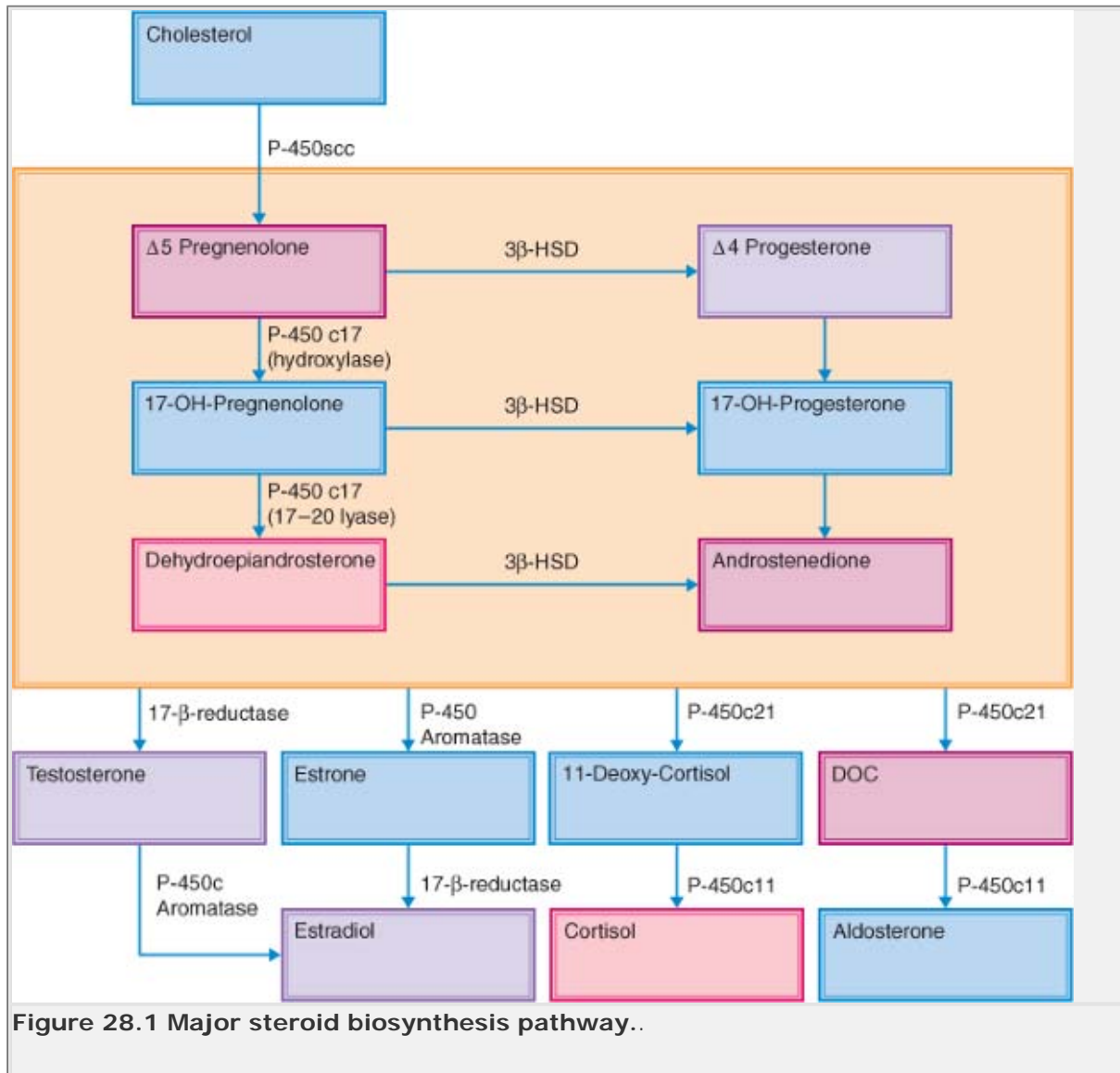
A family history should be obtained to disclose evidence of idiopathic hirsutism, PCOS, congenital or adult onset adrenal hyperplasia (CAH or AOA), diabetes mellitus, and cardiovascular disease. A history of drug use should also be obtained. In addition to drugs that commonly cause hypertrichosis, anabolic steroids and testosterone derivatives may cause hirsutism and even virilization. During the physical examination, attention should be directed to obesity, hypertension, galactorrhea, male-pattern baldness, acne (face and back), and hyperpigmentation. Hirsutism often is the presenting symptom of Cushing syndrome, which may mimic AOA and PCOS. Physical signs of the syndrome include "moon face," plethora, purple striae, dorsocervical and supraclavicular fat pads, and proximal muscle weakness. The preservation or enhancement of the radial musculature, which is present in other hyperandrogenic disorders, may be a useful finding in determining the differential diagnosis.

Role of Androgens

Androgens and their precursors are produced by both the adrenal glands and the ovaries in response to adrenocorticotrophic hormone (ACTH) and luteinizing hormone (LH), respectively (Fig. 28.1). Biosynthesis begins with the rate-limiting conversion of cholesterol to pregnenolone by side-chain cleavage enzyme. Thereafter, pregnenolone undergoes a two-step conversion to the 17-ketosteroid dehydroepiandrosterone (DHEA) along the δ -5 steroid pathway. This conversion is accomplished by

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CYP17, an enzyme with both 17 α -hydroxylase and 17,20-lyase activities. In a parallel fashion, progesterone undergoes transformation to androstenedione in the δ -4 steroid pathway. The metabolism of δ -5 to δ -4 intermediates is accomplished via a δ -5-isomerase, 3 β -hydroxysteroid dehydrogenase (3 β -HSD).



Adrenal 17-Ketosteroids

Secretion of adrenal 17-ketosteroids increases prepubertally, independent of pubertal maturation of the hypothalamic-pituitary-ovarian axis. This alteration in adrenal steroid secretion is termed *adrenarche* and is characterized by a dramatic change in the response of the adrenal cortex to ACTH and preferential secretion of δ -5 steroids, including 17-hydroxyprogesterone, DHEA, and 17-hydroxy progesterone sulfate (DHEAS). The basis for this action is related to the increase in the zona reticularis and in the increased activity of the 17-hydroxylase and the 17,20-lyase enzymes. The increase in adrenal androgens that occurs with adrenarche causes significant increases in the growth of pubic and axillary hair and production of sweat by the axillary pilosebaceous units.

Testosterone

Approximately one half of a woman's serum testosterone is derived from peripheral conversion of secreted androstenedione, and the other half is derived from direct glandular (ovarian and adrenal) secretion. The ovaries and adrenal glands contribute about equally to testosterone production in women. The contribution of the adrenal glands is achieved primarily through secretion of androstenedione.

Approximately 66% to 78% of circulatory testosterone is bound to sex hormone-binding globulin (SHBG) and is considered biologically inactive. Most of the proportion of serum testosterone that is not bound to SHBG is weakly associated with albumin (20%–32%). A small percentage (1%–2%) of testosterone is entirely unbound or free.

The fraction of circulating testosterone that is unbound by SHBG has an inverse relationship with the SHBG concentration. Increased SHBG levels occur in situations associated with high estrogen levels such as pregnancy, the luteal phase, and use of estrogen (including oral contraceptives). Conditions causing elevated thyroid hormone levels and cirrhosis of the liver are associated with reduced fractions of free testosterone, which result from elevated SHBG levels. Conversely, as levels of SHBG decrease, free testosterone fractions increase in response to androgens, which can derive from androgenic disorders (i.e., PCOS, adrenal hyperplasia, Cushing syndrome), medications (i.e., progestational agents with androgenic biologic activities, danazol, glucocorticoids), growth hormone, hyperinsulinemia, obesity, and prolactin.

Assessment of Hyperandrogenemia

In hyperandrogenic states, increases in testosterone production are not proportionately reflected in increased total testosterone levels because of the depression of SHBG levels that occurs concomitant with increasing androgen effects on the liver. Therefore, when moderate hyperandrogenism occurs, which is characteristic of many functional hyperandrogenic states, elevations in total testosterone levels may remain within the normal range, and only free testosterone levels will reveal the hyperandrogenism.

Severe hyperandrogenism, as occurs with virilization and neoplastic production of testosterone, can be detected by measures of total testosterone, however.

Therefore, determination of the total testosterone level in concert with clinical assessment of a patient with hyperandrogenism is frequently sufficient for diagnosis and management. When more precise delineation of the degree of hyperandrogenism is desired, free testosterone levels can be measured to assess increases in testosterone production. Although such measurements are not necessary in evaluating most patients, they are often performed in research and may be useful in some clinical settings.

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Because many practitioners measure some form of testosterone level, they should understand the methods used and their accuracy. Although equilibrium dialysis is the standard technique used for measuring free testosterone, it is expensive, complex, and usually limited to research settings. In a clinical setting, free testosterone levels can be estimated by assessment of testosterone binding to albumin and SHBG.

Testosterone that is nonspecifically bound to albumin (AT) is linearly related to free testosterone (FT) by the following equation:

$$AT = K_a [A] \times FT$$

In this equation, AT is the albumin-bound testosterone, K_a is the association constant of albumin for testosterone, and [A] is the albumin concentration.

In many cases of hirsutism, albumin levels are within a narrow physiologic range and thus do

not significantly affect the concentration of free testosterone. When physiologic albumin levels are present, the free testosterone level can be estimated by measuring total testosterone as well as SHBG. In individuals with normal albumin levels, this method has reliable results compared with those of equilibrium dialysis. It provides a rapid, simple, and accurate determination of the total and calculated free testosterone level as well as the concentration of SHBG.

The level of bioavailable testosterone is based on the relationship of albumin and free testosterone in addition to the levels of actual albumin, total testosterone, and SHBG. This combination of total testosterone, SHBG, and albumin measurements can be used to obtain a more accurate estimate of available bioactive testosterone and thus the androgen effect derived from testosterone (3).

Pregnancy can alter the accuracy of measurements of bioavailable testosterone.

During pregnancy, estradiol, which shares with testosterone a high affinity for SHBG, occupies a large proportion of SHBG binding sites. Thus, measurement of SHBG levels can result in overestimating the binding capacity of SHBG for testosterone. Derived estimates of free testosterone, as opposed to direct measure by equilibrium dialysis, are therefore inaccurate during pregnancy. Testosterone measurements in pregnancy are useful when autonomous secretion of testosterone by tumor or luteoma is suspected. In these instances, total testosterone determinations provide sufficient information for diagnosis.

For testosterone to exert its biologic effects on target tissues, it must be converted into its active metabolite, DHT, by 5 α -reductase (a cytosolic enzyme that reduces testosterone and androstenedione). Two isozymes of 5 α -reductase exist: type 1, which predominates in the skin, and type 2, or acidic 5 α -reductase, which is found in the liver, prostate, seminal vesicles, and genital skin. The type 2 isozyme has a 20-fold higher affinity for testosterone than type 1. Both type 1 and 2 deficiencies in men result in ambiguous genitalia, and both isozymes may play a role in androgen effects on hair growth. Dihydrotestosterone is more potent than testosterone, primarily because of its higher affinity and slower dissociation from the androgen receptor. Although DHT is the key intracellular mediator of most androgen effects, measurements of circulating levels are not clinically useful. **The relative androgenicity of androgens is as follows:.**

- **DHT = 300.**
- **Testosterone = 100.**
- **Androstenedione = 10.**
- **DHEAS = 5.**

Until adrenarche, androgen levels remain low. Around 8 years of age, adrenarche is heralded by a marked increase in DHEA and DHEAS. The half-life of free DHEA is

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extremely short (about 30 minutes) but extends to several hours if DHEA is sulfated. Although no clear role is identified for DHEAS, it is associated with stress, and levels decline steadily throughout adult life. **After menopause, ovarian estrogen secretion ceases, and DHEAS levels continue to decline, whereas testosterone levels are maintained or may even increase.** Although postmenopausal ovarian steroidogenesis contributes to testosterone production, testosterone levels retain diurnal variation, reflecting an ongoing

and important adrenal contribution. Peripheral aromatization of androgens to estrogens increases with age, but because small fractions (2%–10%) of androgens are metabolized in this fashion, such conversion is rarely of clinical significance.

Laboratory Evaluation

When laboratory testing for the assessment of hirsutism is indicated, a bioavailable testosterone level (total testosterone, SHBG, and albumin level) or a calculated free testosterone level (if albumin levels are assumed to be normal) provides the most accurate assessment of the androgen effect derived from testosterone. In most clinical situations, however, total testosterone (less than or equal to 200 ng/mL), DHEAS, and 17-hydroxyprogesterone (17-OHP) measurements can be used to help detect conditions requiring further workup (Table 28.1). When hirsutism is accompanied by absent or abnormal menstrual periods, assessment of LH, follicle-stimulating hormone (FSH), prolactin, and thyroid-stimulating hormone (TSH) values are required to diagnose an ovulatory disorder. Hypothyroidism and hyperprolactinemia may be associated with reduced levels of SHBG and may increase the fraction of unbound testosterone levels, occasionally resulting in hirsutism. Elevated LH:FSH ratios are noted in some women with PCOS, but cannot be used to confirm the diagnosis. In cases of suspected Cushing syndrome, patients should undergo screening with a 24-hour urinary cortisol (most sensitive and specific) assessment or an overnight dexamethasone suppression test. For this test, the patient takes 1 mg of dexamethasone at 11:00 PM, and a blood cortisol assessment is performed at 8:00 AM the next day. Cortisol levels of 2 µg/dL or higher after overnight dexamethasone suppression require a further workup for evaluation of Cushing syndrome. Elevated 17-OHP levels identify patients with AOA and are found in 1% to 5% of hirsute women. Levels of 17-OHP vary significantly within the menstrual cycle, increasing in the periovulatory and luteal phases, and may be modestly elevated in PCOS. Standardized testing requires evaluation in the morning during the follicular phase.

Table 28.1 Normal Values for Serum Androgens^a

Testosterone (total)	20–80 ng/dL
Free testosterone (calculated)	0.6–6.8 pg/mL
Percent free testosterone	0.4–2.4%
Bioavailable testosterone	1.6–19.1 ng/dL
SHBG	18–114 nmol/L
Albumin	3,300–4,800 mg/dL
Androstenedione	20–250 ng/dL
Dehydroepiandrosterone sulfate	100–350 µg/dL
17-hydroxyprogesterone (follicular phase)	30–200 ng/dL

SHBG, sex hormone-binding globulin.

^aNormal values may vary among different laboratories. Free testosterone is calculated using measurements for total testosterone and sex hormone-binding globulin, whereas bioavailable testosterone is calculated using measured total testosterone, sex hormone-binding globulin, and albumin. Calculated values for free and bioavailable testosterone compare well with equilibrium dialysis methods of measuring unbound testosterone when albumin levels are normal. Bioavailable testosterone includes free plus very weakly bound (non-SHBG, nonalbumin) testosterone. Bioavailable testosterone is the most accurate assessment of bioactive testosterone in the serum without performing equilibrium dialysis.

Normal morning baseline follicular phase 17-OHP levels are less than 200 ng/dL (6 nmol/L). When levels are greater than 200 ng/dL but less than 800 ng/dL (24 nmol/L), ACTH testing should be performed to distinguish PCOS from AOA. Levels greater than 800 ng/dL (24 nmol/L) also warrant ACTH testing but are virtually diagnostic of AOA because of 21-hydroxylase deficiency.

Some hirsute women manifest total testosterone levels above normal (20–80 ng/dL [0.723 nmol/L]). Because increased testosterone production is not reliably reflected by total testosterone levels, the diagnosis can be based on the presence of typical male pattern hirsutism or measurement of free or unbound testosterone (bioavailable or calculated free testosterone levels). Total testosterone does, however, serve reliably as a marker for testosterone-producing neoplasms. **Total testosterone levels greater than 200 ng/dL should prompt a workup for ovarian or adrenal tumors, and DHEAS levels greater than twice the upper limit of normal should prompt evaluation for adrenal neoplasm. Both total testosterone and DHEAS should be measured in the presence of virilization.**

In the past, testing for androgen conjugates (e.g., 3 α -androstenediol G [3 α -diol G] and androsterone G [AOG]) as markers for 5 α -reductase activity in the skin) has been advocated. However, routine determination of androgen conjugates to assess hirsute patients is not recommended. Hirsutism itself is an excellent bioassay of free testosterone action on the hair follicle, and androgen conjugates arise from adrenal precursors and are likely markers of adrenal and not ovarian steroid production (4).

In most laboratories, the upper limit of a DHEAS level is 350 μ g/dL (9.5 nmol/L). A random sample is sufficient because the level of variation is minimized as a result of the long half-life characteristic of sulfated steroids. **A normal level essentially rules out adrenal disease, and moderate elevations are a common finding in the presence of PCOS.** A DHEAS level of more than twice the upper limit of normal, 700 μ g/dL (20nmol/L), usually indicates the need to rule out an adrenal tumor or Cushing syndrome. Absolute ceilings for this threshold vary significantly with age, with levels declining steadily after a peak at around age 20 years; laboratories commonly provide reference levels for age. Rarely, ovarian tumors are associated with high DHEAS levels.

Polycystic Ovary Syndrome

The most common cause of hyperandrogenism and hirsutism is PCOS. The association of amenorrhea with bilateral polycystic ovaries and obesity was first described in 1935 by Stein and Leventhal (5) and was known for decades as the Stein-Leventhal syndrome. Subsequently, it is now recognized that **PCOS is a disorder that is characterized principally by oligomenorrhea or amenorrhea with clinical or laboratory evidence of hyperandrogenemia. Furthermore, it is now recognized that a significant proportion of overweight women with PCOS have hyperinsulinemia.** Its origins are likely polygenic or multifactorial or both (6). Following are diagnostic criteria based on the modified consensus of the National Institutes of Health and Child Health and Human Development.

Major

- Chronic anovulation

-

Hyperandrogenemia

-
- **Clinical signs of hyperandrogenism**
-
- **Other etiologies excluded**

Minor

- - **Insulin resistance**
 -
 - **Perimenarchal onset of hirsutism and obesity**
 -
 - **Elevated LH-to-FSH ratio**
-
- - **Intermittent anovulation associated with hyperandrogenemia (free testosterone, DHEAS).**

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In this schema, there are only two major criteria for the diagnosis of PCOS: anovulation and the presence of hyperandrogenism as established by clinical or laboratory means. These features alone are sufficient for the diagnosis in the absence of other pathologies accounting for hyperandrogenism (i.e., AOA, adrenal or ovarian neoplasm, Cushing syndrome) or anovulation (i.e., hypogonadotropic or hypergonadotropic disorders, hyperprolactinemia, thyroid disease).

Other frequently encountered manifestations are less consistent findings and, therefore, qualify only as minor criteria. They include elevated LH:FSH ratio, insulin resistance, oligo-ovulation, perimenarchal onset of hirsutism and obesity, and ultrasonographic evidence of PCOS.

Hirsutism occurs in approximately 70% of patients with PCOS in the United States (7) and in only 10% to 20% of patients with PCOS in Japan (8). A likely explanation for this discrepancy is the genetically determined differences in skin 5 α -reductase activity (9,10).

The menstrual dysfunction that occurs with PCOS arises from anovulation or oligo-ovulation and ranges from amenorrhea to oligomenorrhea. When anovulation is present, it is uncommon for women with PCOS to have regular menses, although one report found that among hyperandrogenic women with regular menstrual cycles, the rate of anovulation is 21% (11). **Classically, the disorder may be lifelong, characterized by abnormal menses from puberty with acne and hirsutism arising in the teens. It may arise in adulthood, concomitant with the emergence of obesity, presumably because obesity is accompanied by increasing hyperinsulinemia** (12).

Obesity occurs in more than 50% of patients with PCOS. The body fat is usually deposited centrally (android obesity). A higher waist-to-hip ratio is associated with insulin resistance, which indicates an increased risk of diabetes mellitus and cardiovascular disease (13).

Insulin resistance, resulting in hyperinsulinemia, is commonly exhibited in PCOS. Insulin resistance may eventually lead to the development of hyperglycemia and type 2 diabetes mellitus (14). About one third of obese PCOS patients have impaired glucose tolerance (IGT), and 7.5% to 10% have type 2 diabetes mellitus (15). These rates are

mildly increased even in nonobese women who have PCOS (10% IGT; 1.5% diabetes) (16), compared with the general population of the United States (7.8% IGT; 1% diabetes) (17).

Abnormal lipoproteins are a common finding in PCOS and include elevated total cholesterol, triglycerides, and low-density lipoproteins (LDL); and low levels of high-density lipoproteins (HDL) and apoprotein A-I (13,18). According to one report, the most characteristic lipid alteration is decreased levels of HDL (19).

Other findings that occur in women with PCOS include impaired fibrinolysis as shown by elevated circulating levels of plasminogen activator inhibitor (20), an increased incidence of hypertension over time that approaches 40% by perimenopause (18), a greater prevalence of atherosclerosis and cardiovascular disease (21,22), and an estimated sevenfold increased risk for myocardial infarction (23).

Pathology

Macroscopically, ovaries in women with PCOS are 2 to 5 times the normal size. A cross-section of the surface of the ovary discloses a white, thickened cortex with multiple cysts that are typically less than a centimeter in diameter. Microscopically, the superficial

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cortex is fibrotic and hypocellular and may contain prominent blood vessels. In addition to smaller atretic follicles, there is an increase in the number of follicles with luteinized theca interna. The stroma may contain luteinized stromal cells (24).

Pathophysiology and Laboratory Findings

The hyperandrogenism and anovulation that accompany PCOS may be caused by abnormalities in four endocrinologically active compartments: (i) the ovaries, (ii) the adrenal glands, (iii) the periphery (fat), and (iv) the hypothalamus-pituitary compartment.

In patients with PCOS, the ovarian compartment is the most consistent contributor of androgens. Dysregulation of CYP17, the androgen-forming enzyme in both the adrenals and the ovaries, may be one of the central pathogenetic mechanisms underlying hyperandrogenism in PCOS (25). The ovarian stroma, theca, and granulosa contribute to ovarian hyperandrogenism and are stimulated by LH (26). This hormone relates to ovarian androgenic activity in PCOS in a number of ways: .

- Total and free testosterone levels correlate directly with LH levels (27).
- The ovaries are more sensitive to gonadotropic stimulation, possibly as a result of CYP17 dysregulation (25).
- Treatment with a gonadotropin-releasing hormone (GnRH) agonist effectively suppresses serum testosterone and androstenedione levels (28).
- Larger doses of a GnRH agonist are required for androgen suppression than for endogenous gonadotropin-induced estrogen suppression (29).

The increased testosterone levels that occur in patients with PCOS are considered ovarian in origin. The serum total testosterone levels are usually no more than twice

the upper normal range (20–80 ng/dL). However, in *ovarian hyperthecosis*, values may reach 200 ng/dL or more (30). The adrenal compartment also plays a role in the development of PCOS. Although the hyperfunctioning CYP17 androgen-forming enzyme coexists in both the ovaries and the adrenal glands, DHEAS is increased in only about 50% of patients with PCOS (31,32). The hyperresponsiveness of DHEAS to stimulation with ACTH (30), the onset of symptoms around puberty, and the observation that 17,20-lyase activation (one of the two CYP17 enzymes) is a key event in adrenarche have led to the hypothesis that PCOS arises as an exaggeration of adrenarche.

The **peripheral compartment**, defined as the skin and the adipose tissue, manifests its contribution to the development of PCOS in several ways: .

- The presence and **activity of 5 α -reductase** in the skin largely **determines the presence or absence of hirsutism** (9,10).
- Aromatase and 17 β -HSD activities are increased in fat cells (33), and **peripheral aromatization is increased** with body weight (34).
- With obesity, the **metabolism of estrogens**, by way of reduced 2-hydroxylation and 17 α -oxidation, **is decreased** (35), and metabolism via estrogen active 16-hydroxyestrogens (estriol) is increased.
- Whereas E₂ is at a follicular phase level in patients with PCOS, **E₁ levels are increased** as a result of peripheral aromatization of androstenedione (36).
- A **chronic hyperestrogenic state**, with reversal of the E₁:E₂ ratio, results and is unopposed by progesterone.

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The **hypothalamic–pituitary compartment** also participates in aspects critical to the development of PCOS: .

- An **increase in LH pulse frequency** relative to those in the normal follicular phase is the result of increased GnRH pulse frequency (37).
- This increase in LH pulse frequency explains the frequent observation of **elevated LH and LH:FSH ratios**.
- **FSH is not increased** with LH, which may result from the combination of increased gonadotropin pulse frequency and the synergistic negative feedback of chronically elevated estrogen levels and normal follicular inhibin.
- About 25% of patients with PCOS exhibit **mildly elevated prolactin levels**, which may result from abnormal estrogen feedback to the pituitary gland. In some patients with PCOS,

administration of *bromocriptine* has reduced LH levels and restored ovulatory function (38).

At present, **genetic studies of PCOS have reported allele sharing in large PCOS patient populations, and linkage studies have focused on candidate genes most likely to be involved in the pathogenesis of PCOS.** Recent linkage reports have identified the *follistatin* (39), *CYP11A* (40), *Calpain 10* (41), *IRS-1* and *IRS-2* regions and loci near the insulin receptor (*19p13.3*) (39,42), *SHBG* (43), and the insulin gene (44) as candidate genes associated with PCOS. Using theca cells derived from women with PCOS, elevated mRNA levels were noted for *CYP11A*, *3BHSD2*, and *CYP 17* genes with corresponding overproduction of testosterone, 17 alpha-hydroxyprogesterone, and progesterone. Despite the characteristically heightened steroidogenesis in PCOS, the *STARB* gene was not found to be overexpressed (39). Recent data derived from theca cells from PCOS women did not identify any genes near the *19p13.3* locus that were differentially expressed; however, the mRNAs of several genes that map to *19p13.3*, including the insulin receptor, *p114-Rho-GEF*, and several expressed sequence tags, were detected in both PCOS and normal theca cells. Those studies further identified new factors that might affect theca cell steroidogenesis and function, including *cAMP-GEFII*, genes involved in all-transretinoic acid (*atRA*) synthesis signaling, genes that participate in the signal transduction pathway, and transcription factor *GATA6*. These findings suggest that a *19p13.3* locus or some other candidate gene may be a signal transduction gene that results in overexpression of a suite of genes downstream that may affect steroidogenic activity (45).

Insulin Resistance

Patients with PCOS frequently exhibit insulin resistance and hyperinsulinemia.

Insulin resistance and hyperinsulinemia participate in the ovarian

steroidogenic dysfunction of PCOS. Insulin alters ovarian steroidogenesis independent of gonadotropin secretion in PCOS. Insulin and insulinlike growth factor I (IGF-I) receptors are present in the ovarian stromal cells. A specific defect in the early steps of insulin receptor-mediated signaling (diminished autophosphorylation) has been identified in 50% of women with PCOS (46).

The most common cause of insulin resistance and compensatory hyperinsulinemia is obesity, but despite its frequent occurrence in PCOS, obesity alone does not alone explain this important association (38). The following observations provide evidence that the insulin resistance associated with PCOS is not the result of hyperandrogenism: .

- Hyperinsulinemia is not a characteristic of hyperandrogenism in general but is uniquely associated with PCOS (47).

- In obese women with PCOS, 30% to 45% have glucose intolerance or frank diabetes mellitus, whereas ovulatory hyperandrogenic women have normal insulin levels and glucose tolerance (47). The associations between PCOS and obesity on the action of insulin appear to be synergistic.
- Suppression of ovarian steroidogenesis with long-acting GnRH analogs in women with PCOS does not change insulin levels or insulin resistance (48).
-

Oophorectomy in patients with hyperthecosis accompanied by hyperinsulinemia and hyperandrogenemia does not change insulin resistance, despite a decrease in androgen levels (49).

***Acanthosis nigricans* is a reliable marker of insulin resistance in hirsute women. This thickened, pigmented, velvety skin lesion is most often found in the vulva and may be present on the axilla, over the nape of the neck, below the breast, and on the inner thigh (50). The HAIR-AN syndrome (46,51) consists of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN).** These patients often have high testosterone levels (>150 ng/dL), fasting insulin levels of greater than 25 μ IU/mL (normal <20 to 24 μ IU/mL), and maximal serum insulin responses to glucose load (75 g) exceeding 300 μ IU/mL (normal <160 μ IU/mL at 2 hours postglucose load).

Screening Strategies for Diabetes and Insulin Resistance

Multiple testing and screening approaches have been proposed to assess the presence of hyperinsulinemia and insulin resistance. In one approach, the fasting glucose:insulin ratio is determined, and values less than 4.5 indicate insulin resistance. Using the 2-hour glucose tolerance test (GTT) with insulin levels, 10% of nonobese and 40% to 50% of obese women with PCOS have impaired glucose tolerance (IGT = 2 hr glucose level \geq 140 or \leq 199 mg/dL) or overt type II diabetes mellitus (any glucose level >200 mg/dL). Some research studies have utilized a peak insulin level of more than 150 μ IU/mL or a mean level of more than 84 μ IU/mL over the three blood draws of a 2-hour GTT as criteria for the diagnosis of hyperinsulinemia (Table 28.2).

The documentation of hyperinsulinemia using either the glucose:insulin ratio or the 2-hour GTT with insulin is problematic. When compared with the standard measure for insulin resistance, the hyperinsulinemic-euglycemic clamp, the glucose:insulin ratio does not always accurately portray insulin resistance. Furthermore, a relative insulin secretion deficit exists in the presence of hyperglycemia. This deficit in appropriate insulin secretion exacerbates the effects of insulin resistance and renders inaccurate the use of hyperinsulinemia as an index of insulin resistance. Thus, routine measurements of insulin levels may not be particularly useful.

Table 28.2 2-Hour Glucose Tolerance Test Results^a

<i>Glucose Levels</i>
Fasting 64–128 mg/dL
1 hour 120–170 mg/dL
2 hour 70–140 mg/dL
<i>2-Hour Glucose Values for Impaired Glucose Tolerance and Type II Diabetes</i>
Normal <140 mg/dL
Impaired = 140–199 mg/dL
Type II Diabetes mellitus \geq 200 mg/dL
^a WHO Criteria, after 75-g glucose load.

Although detection of insulin resistance per se is not of practical importance to the diagnosis or management of PCOS, **testing women with PCOS for glucose intolerance is of value because their risk of cardiovascular disease correlates with this finding.**

An appropriate frequency for such screening depends on age, body mass index, and waist circumference, all of which increase risk.

Interventions

Abnormal glucose metabolism may be significantly improved with weight reduction, which also may reduce hyperandrogenism and restore ovulatory function (52). In obese, insulin-resistant women, caloric restriction that results in weight reduction will reduce the severity of insulin resistance (a 40% decrease in insulin level with a 10-kg weight loss) (53). This decrease in insulin levels should result in a marked decrease in androgen production (a 35% decrease in testosterone levels with a 10-kg weight loss) (54). Exercise also reduces insulin resistance, independent from any associated weight loss, but data on the impact of exercise on the principal manifestations of PCOS are lacking.

Insulin resistance/hyperinsulinemia has been recognized as a cluster syndrome now called the *metabolic syndrome* or *dysmetabolic syndrome X*. Its importance as a risk factor for cardiovascular disease has led to the establishment of diagnostic criteria. Three criteria confirm the diagnosis, and the greater the number of dysmetabolic syndrome X diagnostic criteria present, the higher the level of insulin resistance and its consequences. Patients who may be candidates for treatment with an insulin-lowering agent may be identified by the following diagnostic criteria:

- **Female waist >35 inches.**
- **Triglycerides >150 mg/dL.**
- **HDL cholesterol <50 mg/dL.**
- **Blood pressure >130/85 mm Hg.**
- **Fasting glucose: 110–125 mg/dL.**
- **2-hour GTT (75 g): 140–199 mg/dL.**

Risk factors include non-Caucasian race, sedentary lifestyle, body mass index (BMI) >25, age older than 40 years, cardiovascular disease, hypertension, PCOS, hyperandrogenemia, insulin resistance, HAIR-AN syndrome, nonalcoholic steatohepatosis, and a family history of type II diabetes mellitus or gestational diabetes or impaired glucose tolerance.

Ultrasonographic Studies

Ultrasonographic examination often shows characteristic abnormalities in women with PCOS (55,56). Ovarian size often is increased. **The most important ultrasonographic finding is a bilateral increase in the number of microcysts measuring 0.5 to 0.8 cm, with generally more than five microcysts in any given imaging plane in each ovary.** These findings are neither sufficiently sensitive nor specific to be considered an important part of

the evaluation of women in whom PCOS is suspected.

Long-term Risks

In patients with PCOS who have chronic anovulation, persistently elevated estrogen levels, unopposed by progesterone, increase the risk of endometrial carcinoma (57). These endometrial cancers are usually well-differentiated, stage I lesions with cure rates approaching 100% (see Chapter 33). Endometrial biopsy should be considered in PCOS patients, as they may occasionally have these cancers as early as the third decade of life. Abnormal bleeding, increasing weight, and age are factors that should influence the

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decision to perform endometrial sampling. **Prevention of endometrial cancer is a goal of management in patients with PCOS.** If other dimensions of management do not induce regular ovulation (e.g., clomiphene) or impose continuous progestational influence (e.g., oral contraceptives), regular secretory transformation and menstruation should be induced with periodic administration of a progestational agent. Likewise, the hyperestrogenic state is associated with an increased risk of breast cancer (58) and ovarian cancer (two- to threefold increase) (59). **The risk is greater in nonobese women and those who have not been taking oral contraceptives (OCs).**

Treatment of Hyperandrogenism and PCOS.

Treatment depends on a patient's goals. **Some patients require hormonal contraception, whereas others desire ovulation induction. In all cases in which there is significant ovulatory dysfunction, progestational interruption of unopposed estrogen effects on the endometrium is required.** This may be accomplished by periodic luteal function resulting from ovulation induction, progestational control via contraceptive formulations, or intermittent administration of progestational agents for endometrial or menstrual regulation. **Interruption of the steady state of hyperandrogenism and control of hirsutism usually can be accomplished simultaneously. An exception is those patients desiring pregnancy, in whom effective control of hirsutism may not be possible.** Treatment regimens for hirsutism are listed in Table 28.3. The induction of ovulation and treatment of infertility are discussed in Chapter 30.

Weight Reduction

Weight reduction is the initial recommendation for patients with accompanying obesity because it promotes health; reduces insulin, SHBG, and androgen levels; and may restore ovulation either used alone or in combination with ovulation-induction agents (53). Weight loss of as little as 5% to 7% over a 6-month period can reduce the bioavailable or calculated free testosterone level significantly and restore ovulation and fertility in more than 75% of women (60). Exercise involving large muscle groups

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reduces insulin resistance and can be an important component of nonpharmacologic, lifestyle-modifying management.

Table 28.3 Medical Treatment of Hirsutism

Treatment Category	Specific Regimens
Weight loss	
Hormonal suppression	Oral contraceptives
	Medroxyprogesterone
	Gonadotropin-releasing hormone analogs
	Glucocorticoids
Steroidogenic enzyme inhibitors	Ketoconazole
	5 α -reductase inhibitors
Antiandrogens	Finasteride
	Spiroglactone
	Cyproterone acetate
	Flutamide
Insulin Sensitizer	Metformin
Mechanical	Temporary
	Permanent
	Electrolysis
	Laser hair removal

Oral Contraceptives

Combination OCs decrease adrenal and ovarian androgen production (61,62,63,64) and reduce hair growth in nearly two thirds of hirsute patients. **Treatment with OCs offers the following benefits:**

- The **progestin component suppresses LH**, resulting in diminished ovarian androgen production.
- The **estrogen increases hepatic production of SHBG**, resulting in decreased free testosterone concentration (65,66).
- **Circulating androgen levels are reduced**, including those of DHEAS, which to some extent is independent of the effects of both LH and SHBG (13,67).
- **Estrogens decrease conversion of testosterone to DHT** in the skin by inhibition of 5 α -reductase.

When an OC is used to treat hirsutism, a balance must be maintained between the decrease in free testosterone levels and the intrinsic androgenicity of the progestin. Three progestin compounds that are present in OCs (*norgestrel*, *norethindrone*, and *norethindrone acetate*) are believed to be androgen dominant. The androgenic bioactivity of these steroids may be a factor of their shared structural similarity with 19-nortestosterone steroids (68). Oral contraceptives containing the so-called *new progestins* (*desogestrel*, *gestodene*, *norgestimate*, and *drospirenone*) have minimized androgenic activity. There is limited evidence that there is a difference in clinical outcome determined by these differences in *in vitro* estimates of androgenic potency, however.

The use of OCs alone may be relatively ineffective (less than 10% success rate) in the treatment of hirsutism in women with PCOS (69). Insulin resistance may also be exacerbated by OCs in these patients (70). Therefore, effective protocols for

pharmacologic management of hirsutism with OCs usually include coadministration of agents that impede androgen action.

Medroxyprogesterone Acetate

Oral or intramuscular administration of *medroxyprogesterone acetate* has been used successfully for treatment of hirsutism (71). It directly affects the hypothalamic–pituitary axis by decreasing GnRH production and the release of gonadotropins, thereby reducing testosterone and estrogen production by the ovary. Despite a decrease in SHBG, total and free androgen levels are decreased significantly (72). The recommended oral dosage is 20 to 40 mg daily in divided doses or 150 mg given intramuscularly every 6 weeks to 3 months in the depot form. **Hair growth is reduced in as many as 95% of patients (73).** Side effects of the treatment include amenorrhea, bone mineral density loss, depression, fluid retention, headaches, hepatic dysfunction, and weight gain.

Gonadotropin–releasing Hormone Agonists

Administration of GnRH agonists may allow the differentiation of androgen produced by adrenal sources from that of ovarian sources (29). It has been shown to suppress ovarian steroids to castrate levels in patients with PCOS (74). Treatment with *leuprolide acetate* given intramuscularly every 28 days decreases hirsutism and hair diameter in both idiopathic hirsutism and hirsutism secondary to PCOS (75). Ovarian androgen levels are significantly and selectively suppressed. The addition of OC or estrogen replacement therapy to GnRH agonist treatment (add–back therapy) prevents bone loss and other side effects of menopause, such as hot flushes and genital atrophy. The hirsutism–reducing

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effect is retained (72,76). Suppression of hirsutism is not potentiated by the addition of estrogen therapy to GnRH agonist treatment (77).

Glucocorticoids

Dexamethasone may be used to treat patients with PCOS who have either adrenal or mixed adrenal and ovarian hyperandrogenism. Doses of *dexamethasone* as low as 0.25 mg nightly or every other night are used initially to suppress DHEAS concentrations to less than 400 µg/dL. **Because *dexamethasone* has 40 times the glucocorticoid effect of cortisol, daily doses greater than 0.5 mg every evening should be avoided to prevent the risk of adrenal suppression and severe side effects that resemble Cushing syndrome.** To avoid oversuppression of the pituitary–adrenal axis, morning serum cortisol levels should be monitored intermittently (maintain at >2 µg/dL). Reduction in hair growth rate has been reported (78), as well as significant improvement in acne associated with adrenal hyperandrogenism.

Ketoconazole

Ketoconazole, an antifungal agent approved by the U.S. Food and Drug Administration, inhibits the key steroidogenic cytochromes. Administered at a low dose (200 mg/day), it can significantly reduce the levels of androstenedione, testosterone, and calculated free testosterone (79).

Spirolactone

Spirolactone is a specific antagonist of aldosterone, which competitively binds to the aldosterone receptors in the distal tubular region of the kidney. It is an effective potassium–

sparing diuretic that was originally used for treatment of hypertension. The effectiveness of *spironolactone* in the treatment of hirsutism is based on the following mechanisms: .

- Competitive inhibition of DHT at the intracellular receptor level (9).
- Suppression of testosterone biosynthesis by a decrease in the *CYP* enzymes (80).
- Increase in androgen catabolism (with increased peripheral conversion of testosterone to estrone).
- Inhibition of skin 5 α -reductase activity (9).

Although total and free testosterone levels are significantly reduced in patients with both PCOS and idiopathic hirsutism (hyperandrogenism with regular menses) after treatment with *spironolactone*, total and free testosterone levels in patients with PCOS remain higher than those with idiopathic hirsutism (hyperandrogenism with regular menses) (81). In both groups, SHBG levels are unaltered. The reduction in circulating androgen levels observed within a few days of *spironolactone* treatment partially accounts for the progressive regression of hirsutism.

At least a modest improvement in hirsutism can be anticipated in 70% to 80% of women using at least 100 mg of *spironolactone* daily for 6 months (82). Spironolactone reduces the daily linear growth rate of sexual hair, hair-shaft diameters, and daily hair volume production (83). **The most common dosage is 50 to 100 mg twice daily. Women treated with 200 mg/day show a greater reduction in hair-shaft diameter than women receiving 100 mg/day** (84). Maximal effect on hair growth is noted between 3 and 6 months but continues for 12 months. Electrolysis can be recommended 9 to 12 months after the initiation of *spironolactone* for permanent hair removal.

The most common side effect of *spironolactone* is menstrual irregularity (usually metrorrhagia), which may occur in more than 50% of patients with a dosage of

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200 mg/day (84). Normal menses may resume with reduction of the dosage. Infrequently, other side effects—such as mastodynia, urticaria, or scalp hair loss—occur. Nausea and fatigue can occur with high doses (82). Because *spironolactone* can increase serum potassium levels, its use is not recommended in patients with renal insufficiency or hyperkalemia. Periodic monitoring of potassium and creatinine levels is suggested.

Return of normal menses in amenorrheic patients is reported in as many as 60% of cases (81). Patients must be counseled to use contraception while taking *spironolactone* because it theoretically can feminize a male fetus.

Cyproterone Acetate

Cyproterone acetate is a synthetic progestin derived from 17-OHP that has potent antiandrogenic properties. The primary mechanism of *cyproterone acetate* is competitive inhibition of testosterone and DHT at the level of androgen receptors (80). This agent also induces hepatic enzymes and may increase the metabolic clearance rate of plasma androgens (85). A European formulation of *ethinyl estradiol* with *cyproterone acetate* significantly reduces plasma testosterone and androstenedione levels, suppresses gonadotropins, and increases SHBG levels (86). *Cyproterone acetate* also shows mild glucocorticoid activity (87) and may reduce DHEAS levels (88). Administered in a

reverse sequential regimen (*cyproterone acetate* 100 mg/day on days 5 to 15, and *ethinyl estradiol* 30–50 mg/day on cycle days 5 to 26), this cyclic schedule allows regular menstrual bleeding, provides excellent contraception, and is effective in the treatment of even severe hirsutism and acne (89).

Side effects of *cyproterone acetate* include fatigue, weight gain, decreased libido, irregular bleeding, nausea, and headaches. These symptoms occur less often when *ethinyl estradiol* is added. *Cyproterone acetate* administration has been associated with liver tumors in beagles and is not approved by the U.S. Food and Drug Administration for use in the United States.

Flutamide

Flutamide, a pure nonsteroidal antiandrogen, is approved for treatment of advanced prostate cancer. Its mechanism of action is inhibition of nuclear binding of androgens in target tissues. Although it has a weaker affinity to the androgen receptor than spironolactone or *cyproterone acetate*, larger doses (250 mg given two or three times daily) may compensate for the reduced potency. **Flutamide** is also a weak inhibitor of testosterone biosynthesis.

In a single, 3-month study of *flutamide* alone, most patients demonstrated significant improvement in hirsutism with no change in androgen levels (90). Significant improvement in hirsutism with a significant drop in androstenedione, DHT, LH, and FSH levels was observed in an 8-month follow-up of *flutamide* and low-dose OCs in women who did not respond to OCs alone (91). The side effects of *flutamide* treatment combined with a low-dose OC use included dry skin, hot flashes, increased appetite, headaches, fatigue, nausea, dizziness, decreased libido, liver toxicity, and breast tenderness (92).

In hyperinsulinemic, hyperandrogenemic nonobese adolescents with PCOS taking a combination of *metformin* (850 mg/day) and *flutamide* (62.5 mg/day), a low-dose OC containing *drospirenone* was more effective than an OC with *gestodene* in reducing total and abdominal fat excess (93). The combination of *ethinyl-drospirenone*, *metformin*, and *flutamide* is effective in reducing excess total and abdominal fat as well as attenuating dysadipocytokemia in young women with the hyperinsulinemic PCOS. The antiandrogen *flutamide* appeared to exert critical effects (94).

Many patients taking *flutamide* (50%–75%) report dry skin and a blue-green discoloration of urine. The risk of liver enzyme elevation may preclude *flutamide* as a routine

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option for the treatment of hirsutism. *Flutamide* should not be used in women desiring pregnancy.

Cimetidine

Cimetidine is a histamine H₂ receptor antagonist that has demonstrated a weak antiandrogenic effect as a result of its ability to occupy androgen receptors and inhibit DHT binding at the level of the hair follicles. Although *cimetidine* has been reported to reduce hair growth in women with hirsutism (95), two later studies show no beneficial effect (96,97).

Finasteride

Finasteride is a specific inhibitor of type 2 5 α -reductase enzyme activity that has been approved in the United States at a 5-mg dose for the treatment of benign prostatic hyperplasia and at a 1-mg dose to treat male pattern baldness. In a study in which *finasteride* (5 mg daily) was compared with *spironolactone* (100 mg daily) (98), both drugs resulted in similar significant improvement in hirsutism despite differing effects on androgen levels. Most of

the improvement in hirsutism occurred after 6 months of therapy with 7.5 mg of finasteride daily (99). The improvement in hirsutism in the presence of rising testosterone levels serves as convincing evidence that it is the binding of DHT and not testosterone to the androgen receptor that is responsible for hair growth. *Finasteride* does not prevent ovulation or cause menstrual irregularity. The increase in SHBG caused by OCs further decreases free testosterone levels; OCs used in combination with *finasteride* are more effective in reducing hirsutism than *finasteride* alone. As with *spironolactone* and flutamide, finasteride could theoretically feminize a male fetus; therefore, both of these agents should be used only with additional contraception.

Ovarian Wedge Resection

Bilateral ovarian wedge resection is associated with only a transient reduction in androstenedione levels and a prolonged minimal decrease in plasma testosterone (100,101). In patients with hirsutism and PCOS who have had wedge resection, hair growth was reduced by approximately 16% (5,102). Although Stein's original report cited a pregnancy rate of 85% following wedge resection and maintenance of ovulatory cycles, subsequent reports show lower pregnancy rates and an increased incidence of periovarian adhesions (103).

Laparoscopic Electrocautery

Laparoscopic ovarian electrocautery is used as an alternative to wedge resection in patients with severe PCOS whose condition is resistant to *clomiphene citrate*. In a recent series (104), ovarian drilling was achieved laparoscopically with an insulated electrocautery needle, using 100-W cutting current to aid in entry and 40-W coagulating current to treat each microcyst over 2 seconds (8-mm needle in ovary). In each ovary, 10 to 15 punctures were created. This led to spontaneous ovulation in 73% of patients, with 72% conceiving within 2 years. Of those who had undergone a follow-up laparoscopy, 11 of 15 were adhesion free. To reduce adhesion formation, a technique that cauterized the ovary only in four points led to a similar pregnancy rate (105), with a miscarriage rate of 14%. Most series report a decrease in both androgen and LH concentrations and an increase in FSH concentrations (106,107). Unilateral diathermy has been shown to result in bilateral ovarian activity (108). **The risk of adhesion formation should be discussed with the patient.**

Physical Methods of Hair Removal

Depilatory creams remove hair only temporarily. They break down and dissolve hair by hydrolyzing disulfide bonds. Although depilatories can have a dramatic effect, many women cannot tolerate these irritative chemicals. The topical use of corticosteroid cream may prevent contact dermatitis. *Eflornithine hydrochloride* cream, also known as *difluoromethylornithine (DMFO)*, irreversibly blocks ornithine decarboxylase (ODC), the

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enzyme in hair follicles that is important in regulating hair growth. It also has proved effective in the treatment of unwanted facial hair (109).

Shaving is effective and, contrary to common belief, it does not change the quality, quantity, or texture of hair (110). However, plucking, if done unevenly and repeatedly, may cause inflammation and damage to hair follicles and render them less amenable to electrolysis. Waxing is a grouped method of plucking in which hairs are plucked out from under the skin surface. The results of waxing last longer (up to 6 weeks) than shaving or depilatory creams (110).

Bleaching removes the hair pigment through the use of hydrogen peroxide (usually 6% strength), which is sometimes combined with ammonia. Although hair lightens and softens during oxidation, this method is frequently associated with hair discoloration or skin irritation and is not always effective (109).

Electrolysis and laser hair removal are the only permanent means recommended for hair removal. Under magnification, a trained technician destroys each hair follicle individually. When a needle is inserted into a hair follicle, galvanic current, electrocautery, or both used in combination (blend) destroy the hair follicle. After the needle is removed, a forceps is used to remove the hair. Hair regrowth ranges from 15% to 50%. Problems with electrolysis include pain, scarring, and pigmentation. Cost can also be an obstacle (111). Laser hair removal destroys the hair follicle through photoablation. These methods are most effective after medical therapy has arrested further growth.

Insulin Sensitizers

Because hyperinsulinemia appears to play a role in PCOS-associated anovulation, treatment with insulin sensitizers may shift the endocrine balance toward ovulation and pregnancy, either alone or in combination with other treatment modalities..

Metformin (Glucophage) is an oral biguanide antihyperglycemic drug used extensively for non-insulin-dependent diabetes. Preliminary studies evaluating *metformin* use in pregnancy (category B status) suggest no teratogenicity and a reduced miscarriage rate but a potential increased risk of preeclampsia and perinatal mortality (112,113). *Metformin* lowers blood glucose mainly by inhibiting hepatic glucose production and by enhancing peripheral glucose uptake. *Metformin* enhances insulin sensitivity at the postreceptor level and stimulates insulin-mediated glucose disposal (114). The hyperandrogenism of PCOS is substantially relieved with *metformin* therapy, which leads to a drop in insulin levels and improved reproductive function (115,116,117). *Metformin* (500 mg three times daily) increases ovulation rates both spontaneously and when used in combination with *clomiphene citrate* in obese patients with PCOS. In this group, a 90% ovulation rate has been achieved (118).

In a Cochrane meta-analysis, *metformin* monotherapy improved the ovulation rate 3.9-fold over placebo, and the combination of *metformin* and *clomiphene citrate* improved both the ovulation and pregnancy rates 4.4-fold compared with *clomiphene citrate* use alone (119)..

The most common side effects are gastrointestinal, including nausea, vomiting, diarrhea, bloating, and flatulence. Because the drug has caused fatal lactic acidosis in men with diabetes who have renal insufficiency, baseline renal function testing is suggested (120). The drug should not be given to women with elevated serum creatinine levels (114).

In light of the association between the dysmetabolic syndrome and PCOS, it has been suggested that *metformin* may be an appropriate first-line agent for ovulation induction. Regardless of whether *metformin* is used as a primary ovulation induction agent or in combination with *clomiphene citrate*, **weight loss should be encouraged..**

Current concepts regarding the role of obesity and insulin resistance/hyperinsulinemia in PCOS suggest that the primary intervention should be weight loss (5%–10% of body

weight). In those with an elevated BMI, *orlistat* has proven to be helpful in initiating and maintaining weight loss. **A percentage of PCOS patients will respond to weight loss alone with spontaneous ovulation.** In those who do not respond to weight loss alone or who are unable to lose weight, the sequential addition of *clomiphene citrate* followed by an

insulin sensitizer alone, followed by a combination of these agents, may promote ovulation without the need to proceed to injectable gonadotropin therapy.

The increased incidence of spontaneous abortions in women with PCOS is a prevailing concern. Because of the potential reduction afforded by insulin sensitizers, these agents may be beneficial in combination with gonadotropin therapy for ovulation induction or *in vitro* fertilization (121).

Women with early pregnancy loss have a low level of circulating glycodelin, which has immunomodulatory effects protecting the developing fetus, and of IGF-binding protein (IGFBP)-1. Use of metformin increases levels of both factors, which might explain early findings suggesting it may reduce the high spontaneous abortion rates seen among women with PCOS (122). In an assessment of 68 women treated with *metformin* during pregnancy versus 31 not treated, early pregnancy loss rates were 6/68 versus 13/31, respectively (123). Information regarding an optimal timing for such treatment is unknown.

Cushing Syndrome

The adrenal cortex produces three classes of steroid hormones: glucocorticoids, mineralocorticoids, and sex steroids (androgen and estrogen precursors). Hyperfunction of the adrenal gland can produce clinical signs of increased activity of any or all of these hormones. Increased glucocorticoid action results in nitrogen wasting and a catabolic state. This state causes muscle weakness; osteoporosis; atrophy of the skin with striae, nonhealing ulcerations, and ecchymoses; reduced immune resistance that increases the risk of bacterial and fungal infections; and glucose intolerance resulting from enhanced gluconeogenesis and antagonism to insulin action.

Although most patients with Cushing syndrome gain weight, some lose it. **Obesity is typically central, with characteristic redistribution of fat over the clavicles around the neck and on the trunk, abdomen, and cheeks.** Cortisol excess may lead to insomnia, mood disturbances, depression, and even overt psychosis. With overproduction of sex steroid precursors, women may exhibit hyperandrogenism (hirsutism, acne, oligomenorrhea or amenorrhea, thinning of scalp hair). Masculinization is rare, and its presence suggests an autonomous adrenal origin, most often an adrenal malignancy. With overproduction of mineralocorticoids, patients may manifest arterial hypertension and hypokalemic alkalosis. The associated fluid retention may cause pedal edema.

Characteristic clinical laboratory findings associated with hypercortisolism are confined mainly to a complete blood count showing evidence of granulocytosis and reduced levels of lymphocytes and eosinophils. Increased urinary calcium secretion may be present.

Causes

The six recognized noniatrogenic causes of Cushing syndrome can be divided between those that are ACTH dependent and those that are ACTH independent (**Table 28.4**). The ACTH-dependent causes can result from ACTH secreted by pituitary adenomas or from an ectopic source. The hallmark of ACTH-dependent forms of Cushing syndrome is the presence of normal or high plasma ACTH concentrations with increased cortisol levels. The adrenal glands are hyperplastic bilaterally. Pituitary ACTH-secreting adenoma, or Cushing disease, is the most common cause of Cushing syndrome. **These pituitary adenomas are usually microadenomas (<10 mm in diameter) that may be as small as 1 mm. They behave as if they are resistant, to a variable degree, to the feedback effect of cortisol. As with the normal gland, these tumors secrete**

ACTH in a pulsatile fashion; unlike the normal gland, the diurnal pattern of cortisol secretion is lost. Ectopic ACTH syndrome most often is caused by malignant tumors. About one half of these tumors are small-cell carcinomas of the lung (124). Other tumors include bronchial and thymic carcinomas, carcinoid tumors of the pancreas, and medullary carcinoma of the thyroid.

Table 28.4 Causes of Cushing Syndrome

Category	Cause	Relative Incidence
ACTH-dependent	Cushing syndrome	60% ^a
	Ectopic ACTH-secreting tumors	15%
	Ectopic CRH-secreting tumors	Rare
ACTH-independent	Adrenal cancer	15%
	Adrenal adenoma	10%
	Micronodular adrenal hyperplasia	Rare
	Iatrogenic/factitious	Common

ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone.
^aACTH-dependent Cushing syndrome may be caused by pituitary adenoma, basophil hyperplasia, nodular adrenal hyperplasia, or cyclic Cushing syndrome.

Ectopic corticotropin-releasing hormone (CRH) tumors are rare and include such tumors as bronchial carcinoids, medullary thyroid carcinoma, and metastatic prostatic carcinoma (124). The presence of an ectopic CRH-secreting tumor should be suspected in patients whose dynamic testing suggests pituitary ACTH-dependent disease but who have rapid disease progression and very high plasma ACTH levels.

The most common cause of ACTH-independent Cushing syndrome is exogenous or iatrogenic (i.e., superphysiologic therapy with corticosteroids) or factitious (self-induced). Corticosteroids are used in pharmacologic quantities to treat a variety of diseases with an inflammatory component. Over time, such therapy will result in Cushing syndrome. When corticosteroids are taken by the patient but not prescribed by a physician, the diagnosis may be especially challenging. The diagnostic workup for Cushing syndrome focuses on the ability to suppress autonomous cortisol secretion and determine whether ACTH is elevated or suppressed; it is summarized in Figure 28.2, Tables 28.5, and 28.6 (125,126,127,128,129,130,131).

Treatment of ACTH-independent Forms of Cushing Syndrome

Excluding cases that are of iatrogenic or factitious etiology, ACTH-independent forms of Cushing syndrome are adrenal in origin. Adrenal cancers are usually very large by the time Cushing syndrome is manifest. This is because the tumors are relatively inefficient in the synthesis of steroid hormones. In general, tumors are larger than 6 cm in diameter and are easily detectable by computed tomography (CT) scanning or magnetic resonance imaging (MRI). Adrenal cancers often produce steroids other than cortisol. Thus, when Cushing syndrome is accompanied by hirsutism or virilization in women, or by feminization in men, adrenal cancer should be suspected.

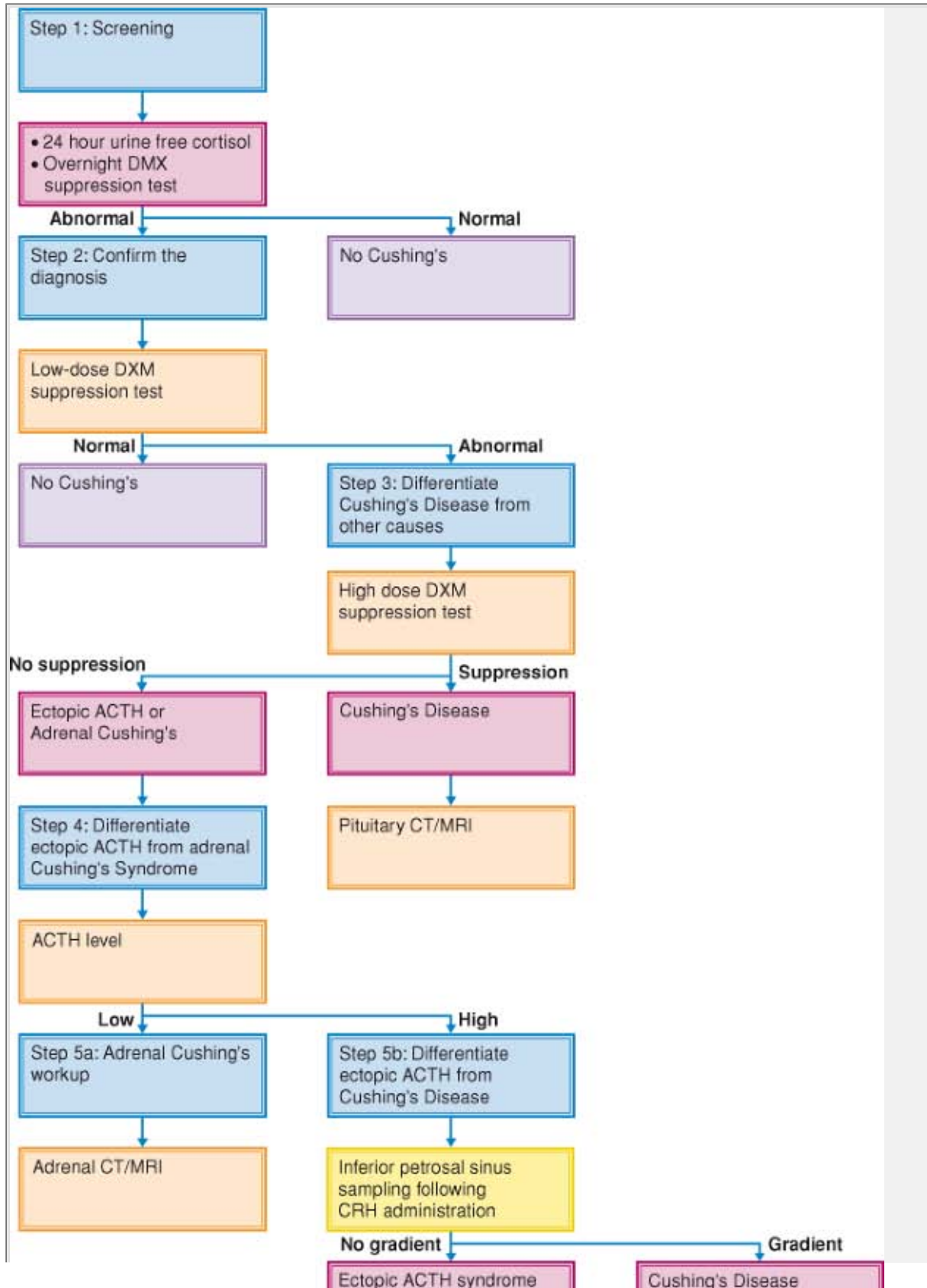
An adrenal tumor that appears large and irregular on radiologic imaging is suggestive of carcinoma. In these cases, a unilateral adrenalectomy through an abdominal exploratory approach is preferable. In most malignant tumors, complete resection is virtually impossible. However, a partial response to postoperative chemotherapy or radiation may

be achieved. Most patients with malignancy die within 1 year. When administered

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immediately after surgery, *mitotane* (*O,P*-DDD, *adrenocorticolytic drug*) may be of benefit in preventing or delaying recurrent disease (132). Manifestations of Cushing syndrome in these patients are controlled by administration of adrenal enzyme inhibitors.



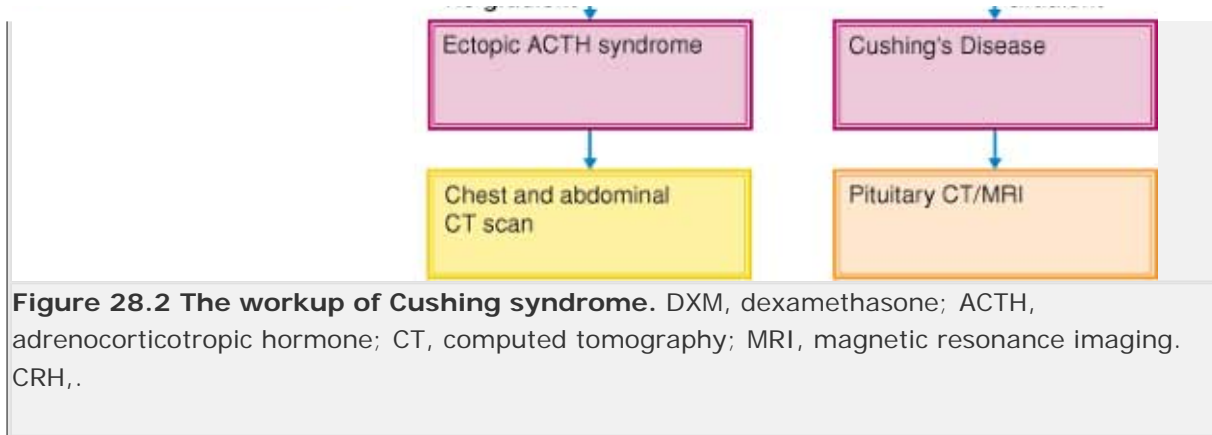


Table 28.5 Diagnostic Workup for Cushing Syndrome

Screening	<p>Women with hirsutism who are suspected of having Cushing syndrome should be tested for urinary free cortisol in a 24-hour collection and should undergo an overnight <i>dexamethasone</i> suppression test. Two consecutive collections are recommended with creatinine determination. Normal urinary free cortisol should range from 30 to 80 $\mu\text{g}/\text{day}$. The overnight <i>dexamethasone</i> suppression test is an 8:00 am cortisol determination after the patient is given 1 mg of <i>dexamethasone</i> at 11:00 PM the previous night.</p>
Confirmation of diagnosis	<p>Confirmation of diagnosis at this stage can be performed by the 2-day, low-dose <i>dexamethasone</i> suppression test of Liddle (117). The patient is given 0.5 mg of <i>dexamethasone</i> every 6 hours for 2 days. A 24-hour urine specimen is collected during the second day. Cushing syndrome is ruled out if there is suppression of urinary 17-hydroxycorticosteroids to $<3 \text{ mg}/24 \text{ hr}$ (or to 0% of baseline), suppression of plasma cortisol to $<4 \mu\text{g}/\text{day}$, or suppression of urinary free cortisol to $<25 \mu\text{g}/24 \text{ hr}$.</p>
Differentiation of Cushing syndrome	<p>The high-dose <i>dexamethasone</i> suppression test is used to differentiate Cushing syndrome from other causes (2 mg every 6 hours). Normally, urinary 17-hydroxycorticoids should be 40% of baseline after 2 days. This test partially suppresses ACTH secretion with a resulting decrease in cortisol production in most patients with Cushing syndrome; however, it has no effect on the majority of patients with ectopic or adrenal Cushing syndrome.</p>
Differentiation of ectopic ACTH syndrome	<p>High plasma ACTH ($>4.5 \text{ pmol}/\text{L}$ or $>20 \text{ pg}/\text{mL}$) is consistent with ectopic ACTH production from adrenal glands. A low ACTH level ($<1.1 \text{ pmol}/\text{L}$ or $<5 \text{ pg}/\text{mL}$) identifies a patient who most likely has adrenal Cushing syndrome.</p>

ACTH-independent and -dependent.

A patient with ACTH-independent Cushing syndrome should undergo an adrenal scan by MRI and should be prepared for adrenal surgery. A patient with ACTH-dependent Cushing syndrome should initially receive an administration of cortisol-releasing hormone (1 µg/kg IV over 1 minute), which is followed 3–5 minutes later by simultaneous sampling of both the inferior petrosal sinuses and of the peripheral vein. The ratio of ACTH levels from the inferior petrosal sinuses to peripheral plasma is then calculated. An inferior petrosal sinus is virtually diagnostic of a pituitary tumor. Moreover, 95% of patients with Cushing syndrome are found to have ratios higher than 2. If the test indicates a patient has Cushing syndrome, a pituitary MRI with gadolinium enhancement should be obtained in preparation for transsphenoidal surgery. If the results indicate ectopic ACTH secretion, a CT scan of the chest and possibly the abdomen should be performed.

ACTH, adrenocorticotrophic hormone; IV, intravenous; MRI, magnetic resonance imaging; CT, computed tomography.

Adrenal adenomas are smaller than carcinomas and average 3 cm in diameter.

These tumors are usually unilateral and infrequently are associated with other steroid-mediated syndromes. Micronodular adrenal disease is a disorder of children, adolescents, and young adults. The adrenal glands contain numerous small (>3 mm) nodules, which often are pigmented and secrete sufficient cortisol to suppress pituitary ACTH. This condition can be sporadic or familial.

Surgical removal of a neoplasm is the treatment of choice (133,134). If a unilateral, well-circumscribed adenoma is identified by MRI or CT scanning, the flank approach may be the most convenient. The cure rate following surgical removal of adrenal adenomas approaches 100%. Because normal function of the hypothalamic-pituitary-adrenal axis is suppressed by autonomous cortisol production, cortisol replacement should follow

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surgery. The dosage is titrated downward over several months, during which recovery of normal adrenal function is monitored.

Table 28.6 Laboratory Diagnosis of Cushing Syndrome

Diagnosis	24-Hour Urinary Cortisol	DEX Low-Dose	DEX High-Dose	ACTH
ACTH-dependent				
Cushing syndrome (60%)	Increased	Increased	Decreased	Normal
Pituitary adenoma				
Basophil hyperplasia				
Nodular adrenal hyperplasia				
Cyclic Cushing syndrome				
Ectopic ACTH (15%)	Increased	Increased	Increased	Increased
Ectopic CRH (rare)	Increased	Increased	Increased or decreased	Increased
ACTH-independent				

Adrenal neoplasia	Increased	Increased	Increased	Decreased
Adenoma (10%)				
Carcinoma (15%)				
Primary adrenocorticoid nodular dysplasia (<1%)>				
Pseudo-Cushing syndrome (alcohol-related, <1%)	Increased	Increased	Decreased	Normal
Exogenous glucocorticoids/factitious (not cortisol)	Increased or Decreased	Decreased	Decreased	Decreased
DEX, dexamethasone; ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone.				

Treatment of Cushing Disease

The treatment of choice for Cushing disease is transsphenoidal resection. The cure rate is approximately 80% in patients with microadenomas who undergo surgery (128) and is less than 50% in patients with macroadenomas (129). Following surgery, transient diabetes insipidus and enduring compromise of anterior pituitary secretion of growth hormone, gonadotropins, and TSH are common (130).

Radiation Therapy

High-voltage external pituitary radiation (4,200–4,500 cGy) is given at a rate not exceeding 200 cGy/day. Although only 15% to 25% of adults show total improvement (130), approximately 80% of children respond (131).

Medical Therapy

Mitotane can be used to induce medical adrenalectomy during or after pituitary radiation (132). The role of medical therapy is to prepare the severely ill patient for surgery and to maintain normal cortisol levels while a patient awaits the full effect of radiation. Occasionally, medical therapy is used for patients who respond to therapy with only partial remission. Adrenal enzyme inhibitors include *aminoglutethimide*, *metyrapone*, *trilostane*, and *etomidate*.

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A combination of *aminoglutethimide* and *metyrapone* may cause a total adrenal enzyme block requiring corticosteroid-replacement therapy. *Ketoconazole* also inhibits adrenal steroid biosynthesis at the side arm cleavage and 11 β -hydroxylation steps. The dose of *ketoconazole* for adrenal suppression is 600 to 800 mg/day for 3 months to 1 year (135). *Ketoconazole* is effective for long-term control of hypercortisolism of either pituitary or adrenal origin.

Nelson syndrome results from adenomatous progression of ACTH-secreting cells in patients with Cushing syndrome treated by bilateral adrenalectomy. The macroadenoma that causes this syndrome produces sellar pressure symptoms of headaches, visual field disturbances, and ophthalmoplegia. Extremely high ACTH levels in Nelson syndrome are associated with severe hyperpigmentation (melanocyte-stimulating hormone activity). The treatment is surgical removal or radiation. The offending adenomatous tissue is often resistant to complete surgical removal (136). This syndrome reportedly complicates 10% to 50% of bilateral adrenalectomy cases. Nelson syndrome is less common today because bilateral adrenalectomy is less frequently used as initial treatment.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is transmitted as an autosomal recessive disorder. Several adrenocortical enzymes necessary for cortisol biosynthesis may be affected. Failure to synthesize the fully functional enzyme has the following effects: .

- A relative decrease in cortisol production.
- A compensatory increase in ACTH levels.
- Hyperplasia of the zona reticularis of the adrenal cortex.
- An accumulation of the precursors of the affected enzyme in the bloodstream.

21-Hydroxylase Deficiency

Deficiency of 21-hydroxylase is responsible for more than 90% of cases of adrenal hyperplasia resulting from adrenal synthetic enzyme deficiency. The disorder produces a spectrum of conditions of CAH, with or without salt wasting, and milder forms that are expressed as hyperandrogenism of pubertal onset (AOAH). Salt-wasting CAH, the most severe form, affects 75% of patients with congenital manifestations during the first 2 weeks of life, and results in a life-threatening hypovolemic salt-wasting crisis, accompanied by hyponatremia, hyperkalemia, and acidosis. The salt-wasting form arises from a severity of enzyme deficiency sufficient to result in ineffective aldosterone synthesis. With or without salt-wasting and newborn adrenal crisis, the condition is usually diagnosed earlier in affected female newborns than in male newborns because genital virilization (e.g., clitoromegaly, labioscrotal fusion, and abnormal urethral course) is apparent at birth.

In simple virilizing CAH, affected patients are diagnosed as virilized newborn girls or as rapidly growing masculinized boys at 3 to 7 years of age. The diagnosis is based on basal levels of the substrate for 21-hydroxylase, 17-hydroxyprogesterone (17-OHP) in cases of congenital adrenal hyperplasia caused by 21 hydroxylase deficiency. In milder forms of the disorder with manifestations later in life (acquired, late-onset, or adult-onset adrenal hyperplasia), the diagnosis depends on basal and ACTH-stimulated levels of 17-OHP.

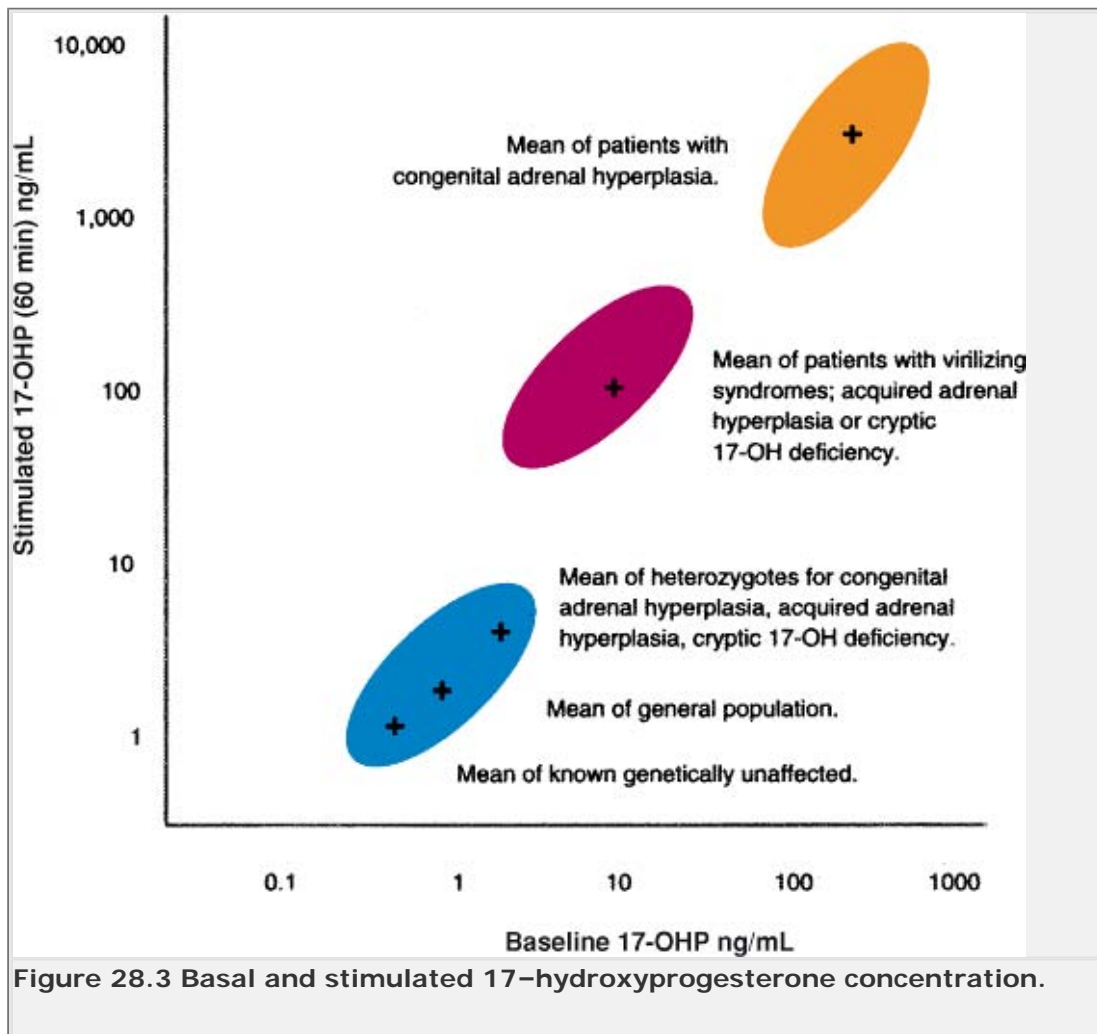
- Basal follicular phase 17-OHP less than 200 ng/dL virtually excludes the disorder; no further testing is required.
- Basal 17-OHP greater than 500 ng/dL establishes the diagnosis; there is no need for further testing (137).
- Basal 17-OHP greater than 200 ng/dL and less than 500 ng/dL requires ACTH stimulation testing.
- In the ACTH stimulation test, plasma levels of 17-OHP are checked 1 hour following

intravenous administration of a bolus of 0.25 mg ACTH 1–24 (*cosyntropin* [*Cortrosyn*]) (Fig. 28.3). 17–OHP levels after ACTH stimulation in adult–onset adrenal hyperplasia are generally greater than 1,000 ng/dL (137) (see Fig. 28.3).

Individuals who are heterozygous (carriers) for both adult–onset adrenal hyperplasia and CAH reveal stimulated 17–OHP values less than 1,000 ng/dL. In many cases, an overlap with the values seen in the normal population is observed (138) (see Fig. 28.3).

Nonclassic Adult–onset Congenital Adrenal Hyperplasia

The nonclassic type of 21–hydroxylase deficiency represents partial deficiency in 21–hydroxylation, which produces a late–onset, milder hyperandrogenemia. Its occurrence depends on some degree of functional deficit resulting from mutations affecting both alleles for the 21–hydroxylase enzyme. Heterozygote carriers for mutations in the 21–hydroxylase enzyme will demonstrate normal basal and modestly elevated stimulated levels of 17–OHP but no abnormalities in circulating androgens. Some women with a mild gene defects in both alleles demonstrate modest elevations in circulating 17–OHP concentrations but no clinical symptoms or signs.



The hyperandrogenic symptoms of AOAHA are mild and typically present during or after puberty. Following are the three phenotypic varieties (137):.

- Those with ovulatory abnormalities and features consistent with PCOS (39%).
- Those with hirsutism alone without oligomenorrhea (39%).
- Those with elevated circulating androgens but without symptoms (cryptic) (22%).

The need for screening patients with hirsutism for adult-onset adrenal hyperplasia depends on the patient population. The frequency of some form of the disorder varies by ethnicity and is estimated at 0.1% of the general population, 1% to 2% of Hispanics and Yugoslavs, and 3% to 4% of Ashkenazi Jews (139).

Genetics of 21-Hydroxylase Deficiency

- The 21-hydroxylase gene is located on the short arm of chromosome 6, in the midst of the HLA region.
- The 21-hydroxylase gene is now termed *CYP21*. Its homologue is the pseudogene *CYP21P* (140).
- Because *CYP21P* is a pseudogene, the lack of transcription renders it nonfunctional. The *CYP21* is the active gene.
- The *CYP21* gene and the *CYP21P* pseudogene alternate with two genes called *C4B* and *C4A*, both of which encode for the fourth component (*C4*) of serum complement (140).
- The close linkage between the 21-hydroxylase genes and *HLA* alleles has allowed the study of 21-hydroxylase inheritance patterns in families through blood *HLA* typing (e.g., linkage of *HLA-B14* was found in Ashkenazi Jews, Hispanics, and Italians) (141).

Prenatal Diagnosis and Treatment

Women with congenital and adult-onset forms of the disorder are at a significant risk for having affected infants because of the high frequency of mutations in 21-hydroxylase mutations in the general population. This fact represents an important rationale for screening hyperandrogenic women for this disorder if they anticipate childbearing. **In families at risk for CAH, and in instances in which one partner expresses the congenital or adult-onset form of the disease, first-trimester prenatal screening using chorionic villus sampling is advocated** (140). Currently, the fetal DNA is used for specific amplification of the *CYP21* gene using polymerase chain reaction (PCR) (142). When there is evidence of fetal involvement, an aggressive and controversial approach involves the use of **dexamethasone treatment for all pregnant women at risk of having a child with CAH.** The dosage is 20 mg/kg in three divided doses administered as soon as pregnancy is recognized and no later than 9 weeks of gestation. This is done before performing chorionic villus sampling or amniocentesis in the second trimester. *Dexamethasone* crosses the placenta and

suppresses ACTH in the fetus. If the fetus is found to be an unaffected female or a male, treatment is discontinued. If the fetus is an affected female, *dexamethasone* therapy is continued. When *dexamethasone* is administered before 9 weeks of gestation and is continued to term, it effectively reduces genital ambiguity in genetic females (140). However, **at least two thirds of treated females may still require surgical repair of the genitalia.** Although prenatal treatment reduces

virilization in females, the efficacy and safety to both mother and baby have not been verified, and the unnecessary treatment of seven of every eight pregnancies poses a ethical dilemma (143).

11 β -Hydroxylase Deficiency

In a small percentage of patients with CAH, hypertension rather than mineralocorticoid deficiency develops. The hypertension responds to corticosteroid replacement (144). Most of these patients have a deficiency in 11 β -hydroxylase. In most populations, 11 β -hydroxylase deficiency accounts for 5% to 8% of the cases of CAH, or 1 in 100,000 births (145). A much higher incidence, 1 in 5,000 to 7,000, has been described in Moroccan Jewish immigrants (146).

Two 11 β -hydroxylase isoenzymes, *CYP11-B1* and *CYP11-B2*, are responsible for synthesis of cortisol and aldosterone, respectively,. They are encoded by two genes on the middle of the long arm of chromosome 8 (147,148).

Inability to synthesize a fully functional 11 β -hydroxylase enzyme causes a decrease in cortisol production, a compensatory increase in ACTH secretion, and increased production of androstenedione, 11-deoxycortisol, 11-deoxycorticosterone, and DHEA. The diagnosis of 11 β -hydroxylase-deficient late-onset adrenal hyperplasia is determined when 11-deoxycortisol levels are higher than 25 ng/mL 60 minutes after ACTH 1-24 stimulation (149).

Patients with 11 β -hydroxylase deficiency may present with either a classic pattern of the disorder or symptoms of a mild deficiency. The severe, classic form is found in about two thirds of the patients with mild-to-moderate hypertension during the first years of life. In about one third of the patients, it is associated with left ventricular hypertrophy, with or without retinopathy, and death is occasionally reported from cerebrovascular accident (144). Signs of androgen excess are common in the severe form and are similar to those seen in the 21-hydroxylase deficiency.

In the mild, nonclassic form, children are found to have virilization or precocious puberty but not hypertension. Adult women seek treatment for postpubertal onset of hirsutism, acne, and amenorrhea.

3 β -Hydroxysteroid Dehydrogenase Deficiency

Deficiency of 3 β -hydroxysteroid dehydrogenase occurs with varying frequency in hirsute patients (150,151). The enzyme is found in both the adrenal glands and ovaries (unlike 21- and 11-hydroxylase) and is responsible for transforming δ -5 steroids into the corresponding δ -4 compounds, a step integral to the synthesis of glucocorticoids, mineralocorticoids, as well as testosterone and estradiol. In severe forms, cortisol and mineralocorticoids are deficient. In mild forms, elevated ACTH levels overcome these critical deficiencies, and the diagnosis of this disorder relies on the relationship of δ -5 and δ -4 steroids. A marked elevation of DHEA and DHEAS in the presence of normal or mildly elevated testosterone or androstenedione may be a signal to initiate a screening protocol for 3 β -hydroxysteroid dehydrogenase deficiency using exogenous ACTH stimulation (150). Following intravenous administration of a 0.25-mg ACTH 1-24 bolus, 17-hydroxypregnenolone levels rise significantly within 60 minutes in women

with 3 β -hydroxysteroid dehydrogenase deficiency compared with normal women (2,276 ng/dL compared with normal of 1,050 ng/dL). The mean poststimulation ratio between 17-hydroxypregnenolone and 17-OHP is markedly elevated (mean ratio of 11 compared with 3.4 in normal controls and 0.4 in 21-hydroxylase deficiency). Because of the rarity of this disorder, routine screening of hyperandrogenic patients is not justified (150,151).

Treatment of Adult-onset Congenital Adrenal Hyperplasia

In adults with CAH, dexamethasone has been shown to suppress the hypothalamic-pituitary axis better than cortisone acetate or hydrocortisone administered in equivalent doses. It also may induce less fluid retention than other corticosteroids. Evening administration with a dosage of 0.25 to 0.5 mg is most effective (152). In some patients, alternate-day therapy using the same dosage is sufficient. Periodic evaluation of serum cortisol is recommended. If morning serum cortisol concentrations are maintained at greater than 2 μ g/dL, oversuppression, with consequent impaired hypothalamic-pituitary-adrenal responsiveness to acute stress, is unlikely (153). Many patients with AOA undoubtedly are treated, undiagnosed, with therapies for ovarian hyperandrogenism or PCOS, with progestins for endometrial regulation, *clomiphene citrate* or gonadotropins for ovulation induction, or progestins and antiandrogens for control of hirsutism. These therapies may be appropriate as an alternative to glucocorticoid therapy, even when AOA is recognized as the cause for the patient's symptoms.

Androgen-secreting Ovarian and Adrenal Tumors

Patients with severe hirsutism, virilization, or recent and rapidly progressing signs of androgen excess require careful investigation for the presence of an androgen-secreting neoplasm. In prepubertal girls, virilizing tumors may cause signs of heterosexual precocious puberty in addition to hirsutism, acne, and virilization. All patients with rapidly progressing or severe hyperandrogenism should undergo determination of levels of testosterone and DHEAS. A markedly elevated total testosterone level (2.5 times the upper normal range or >200 ng/dL) is typical of an ovarian androgen-secreting tumor, and a DHEAS level greater than 800 μ g/dL is typical of an adrenal tumor. An adrenal tumor is unlikely when serum DHEAS and urinary 17-ketosteroid excretion measurements are in the normal basal range and the serum cortisol concentration is less than 3.3 μ g/dL after *dexamethasone* administration (154). The results of other dynamic tests, especially testosterone suppression and stimulation, are unreliable (155).

A vaginal and abdominal ultrasonographic examination is the first step in the evaluation of findings suggesting ovarian neoplasm. Duplex Doppler scanning may increase the accuracy of tumor diagnosis and localization (156).

Computed tomography scanning can reveal tumors larger than 10 mm (1 cm) in the adrenal gland but may not help to distinguish among different types of solid tumors or benign incidental nodules (157). In the ovaries, CT scanning cannot help differentiate hormonally active from functional tumors (156,157).

Magnetic resonance imaging is comparable, if not superior, to CT scanning in detecting ovarian neoplasms, but it is neither more sensitive than high-quality ultrasonography nor more useful in clinical decision making when a likely neoplasm is identified by ultrasonography. Nuclear medicine imaging of the abdomen and pelvis after injection with NP-59 ([¹³¹-iodine] 6- β -iodomethyl-19-norcholesterol), preceded by adrenal and thyroid suppression, may facilitate tumor localization (150). In the rare circumstances when

imaging fails to provide clear evidence of a neoplastic source of excess androgens, selective venous catheterization with measurement of site-specific androgen levels to identify an occult source of androgen excess may be utilized (158). If all four vessels are catheterized transfemorally, selective venous catheterization allows direct localization of the tumor. Samples are obtained for hormonal analysis, with positive localization defined as a 5:1 testosterone gradient compared with lower vena cava values (159). Under such circumstances, specificity approaches 80%, but this rate should be weighed against the 5% rate of significant complications, such as adrenal hemorrhage and infarction, venous thrombosis, hematoma, and radiation exposure (160).

Androgen-producing Ovarian Neoplasms

Ovarian neoplasms are the most frequent androgen-producing tumors. *Granulosa cell tumors* constitute 1% to 2% of all ovarian tumors and occur mostly in adult women (in postmenopausal more frequently than in premenopausal women) (see Chapter 35). Usually associated with estrogen production, they are the most common functioning tumors in children and lead to isosexual precocious puberty (161). Total abdominal hysterectomy and bilateral salpingo-oophorectomy are the treatments of choice. If fertility is desired, in the absence of contralateral ovarian or pelvic node involvement, unilateral salpingo-oophorectomy is justifiable. The malignant potential of these lesions is variable. The 10-year survival rates vary from 60% to 90%, depending on the stage, tumor size, and histologic atypia (161).

Thecomas are rare and occur in older patients. In one study, only 11% were found to be androgenic, even in the presence of steroid-type cells (luteinized thecomas) (161). The tumor is rarely malignant and rarely bilateral, and a simple oophorectomy is sufficient treatment.

Sclerosing stromal tumors are benign neoplasms that usually occur in patients younger than 30 years (161). A few cases with estrogenic or androgenic manifestations have been reported.

Sertoli-Leydig cell tumors, previously classified as androblastoma or arrhenoblastoma, account for 11% of solid ovarian tumors. They contain various proportions of Sertoli cells, Leydig cells, and fibroblasts (161). Sertoli-Leydig cell tumors are the most common virilizing tumors in women of reproductive age; however, masculinization occurs in only one third of patients. The tumor is bilateral in 1.5%. In 80% of cases, it is diagnosed at stage IA (161). Treatment with unilateral salpingo-oophorectomy is justified in patients with stage IA disease who desire fertility. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and adjuvant therapy are recommended for postmenopausal women who have advanced-stage disease.

Pure Sertoli cell tumors are usually unilateral. For a premenopausal woman with stage I disease, a unilateral salpingo-oophorectomy is the treatment of choice. Malignant tumors are rapidly fatal (162).

Gynandroblastomas are benign tumors with well-differentiated ovarian and testicular elements. A unilateral oophorectomy or salpingo-oophorectomy is sufficient treatment.

Sex cord tumors with annular tubules (SCTATs) are frequently associated with Peutz-Jeghers syndrome (gastrointestinal polyposis and mucocutaneous melanin pigmentation) (163). Their morphologic features range between those of the granulosa cell and Sertoli cell tumors. Whereas SCTATs with Peutz-Jeghers syndrome tend to be bilateral and benign, SCTATs without Peutz-Jeghers syndrome are almost always unilateral and are malignant in one fifth of cases (161).

Steroid Cell Tumors

Steroid cell tumors are composed entirely of steroid-secreting cells subclassified into stromal luteoma, Leydig cell tumors (hilar and nonhilar), and steroid cell tumors that are not otherwise specific (161). Virilization or hirsutism is encountered with three fourths of Leydig cell tumors, with one half of steroid cell tumors that are not otherwise specific, and with 12% of stromal luteomas.

Nonfunctioning Ovarian Tumors

Ovarian neoplasms that do not directly secrete androgens are occasionally associated with androgen excess resulting from secretion by adjacent ovarian stroma. Such tumors include serous and mucinous cystadenomas, Brenner tumors, Krukenberg tumors, benign cystic teratomas, and dysgerminomas (164). Gonadoblastomas arising

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in the dysgenetic gonads of patients with a Y chromosome may be associated with androgen and estrogen secretion (165,166).

Stromal Hyperplasia and Stromal Hyperthecosis

Stromal hyperplasia is a nonneoplastic proliferation of ovarian stromal cells. *Stromal hyperthecosis* is defined as the presence of luteinized stromal cells at a distance from the follicles (167).

Stromal hyperplasia, which is typically seen in patients between 60 and 80 years of age, may be associated with hyperandrogenism, endometrial carcinoma, obesity, hypertension, and glucose intolerance (167). *Hyperthecosis* also is seen in a mild form in older patients. In patients of reproductive age, hyperthecosis may demonstrate severe clinical manifestations of virilization, obesity, and hypertension. Hyperinsulinemia and glucose intolerance may occur in as many as 90% of patients with hyperthecosis and may play a role in the etiology of stromal luteinization and hyperandrogenism (50). Hyperthecosis is found in many patients with hyperandrogenemia, insulin resistance, and acanthosis nigricans (HAIR-AN syndrome).

In patients with hyperthecosis, levels of ovarian androgens, including testosterone, DHT, and androstenedione are increased, usually in the male range. The predominant estrogen, as in PCOS, is estrone, which is derived from peripheral aromatization. The $E_1:E_2$ ratio is increased. Unlike in PCOS, gonadotropin levels are normal (168).

Wedge resection for the treatment of mild hyperthecosis has been successful and has resulted in resumption of ovulation and even in a pregnancy (169). However, in cases of more severe hyperthecosis and high total testosterone levels, the ovulatory response to wedge resection is only transient (168). In a study in which bilateral oophorectomy was used to control severe virilization, hypertension and glucose intolerance sometimes disappeared (170). Moreover, when a GnRH agonist was used to treat patients with severe hyperthecosis, ovarian androgen production was dramatically suppressed (171).

Virilization during Pregnancy

Luteomas of pregnancy are frequently associated with maternal and fetal masculinization. This is not a true neoplasm but rather a reversible hyperplasia, which usually regresses postpartum. A review of the literature reveals a 30% incidence of maternal virilization and a 65% incidence of virilized female newborns in the presence of a pregnancy luteoma and maternal masculinization (172).

Other tumors causing virilization in pregnancy include (in descending order of frequency) Krukenberg tumors, mucinous cystic tumors, Brenner tumors,

serous cystadenomas, endodermal sinus tumors, and dermoid cysts (161).

Virilizing Adrenal Neoplasms

The most common virilizing adrenal neoplasms are adrenal carcinomas. When these malignancies virilize, they are invariably associated with elevations in DHEAS, which are usually accompanied by hypercortisolism. These tumors often are large and detectable on abdominal examination. Less commonly, the adrenals are the site for testosterone-secreting adenomas. Therefore, high testosterone levels (in the tumor range), accompanied by normal or only moderately elevated DHEAS levels, should not divert attention from the adrenal gland to the ovary. In fact, patients with these adenomas manifest increased testosterone production following stimulation with human chorionic gonadotropin (hCG) or LH and decreased testosterone secretion following LH suppression.

Of the fewer than 100 reported cases of pure virilizing adrenal neoplasms, 90% were benign. Although the peak age for the diagnosis of adenomas was 20 to 40 years, most of

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the pure testosterone-producing tumors occurred in menopausal women. With one exception, all cases of adenomas were unilateral. Fifty percent were palpable abdominally in children; in adults, none was detected solely by physical examination (173).

Prolactin Disorders

Prolactin was first identified as a product of the anterior pituitary in 1933 (174). Since that time, it has been found in nearly every vertebrate species. Its presence in humans was long inferred by the association of the syndrome of amenorrhea and galactorrhea in the presence of pituitary macroadenomas, although it was not definitively identified as a human hormone until 1971. The specific activities of human prolactin (hPRL) were defined initially by the separation of its activity from growth hormone (175) and subsequently by radioimmunoassay (176,177). **Although the initiation and maintenance of lactation is the primary function of prolactin, many studies have documented roles for prolactin activity both within and beyond the reproductive system.**

Prolactin Secretion

There are 199 amino acids within human prolactin, with a molecular weight (MW) of 23,000 daltons (Fig. 28.4). Although human growth hormone and placental lactogen have significant lactogenic activity, they have only a 16% and 13% amino acid sequence homology with prolactin, respectively. In the human genome, a single gene on chromosome 6 encodes prolactin. The prolactin gene (*10 kb*) has five exons and four introns. Its transcription is regulated in the pituitary by a proximal promoter region and in extrapituitary locations by a more upstream promoter (178).

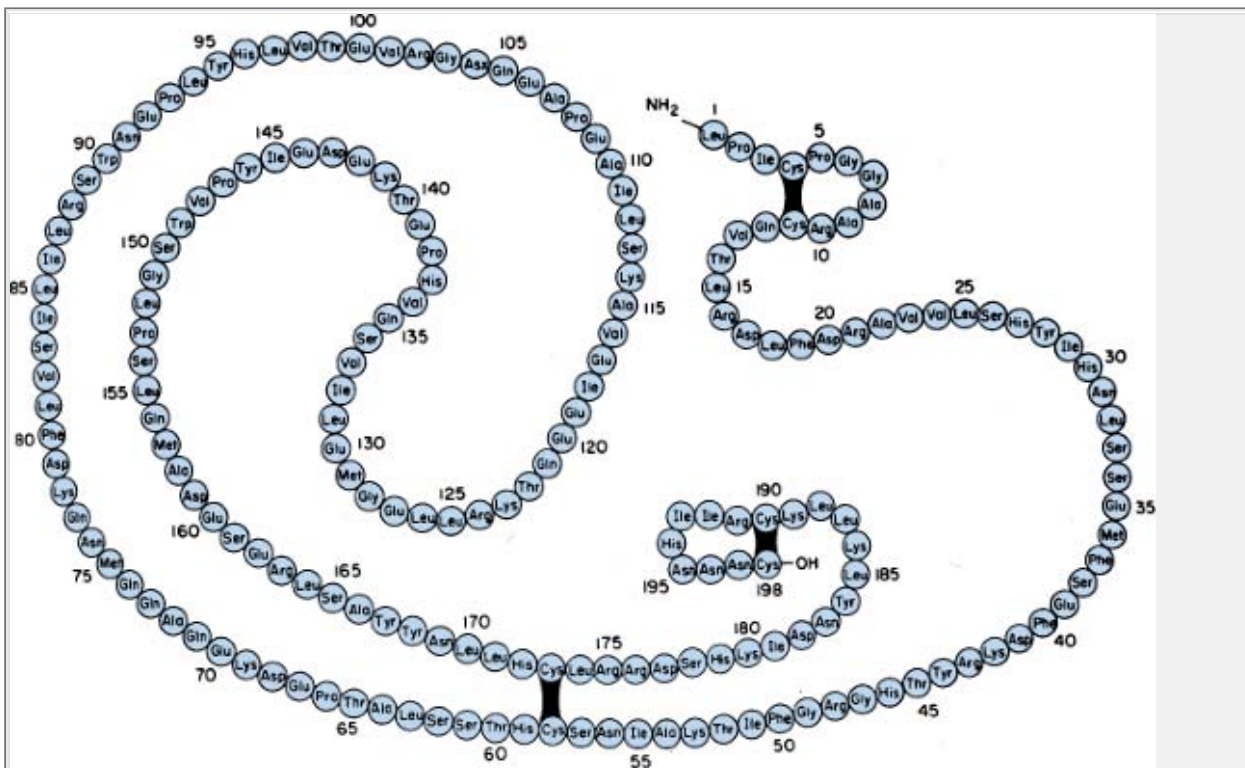


Figure 28.4 Amino acid sequence of prolactin. Three cysteine disulfide bands are located within the molecule. (From **Bondy PK.** *Rosenberg leukocyte esterase: metabolic control and disease.* 8th ed. Philadelphia, PA: WB Saunders, 1980, with permission.).

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In the basal state, three forms are released, a monomer, a dimer, and a multimeric species, called *little*, *big*, and *big-big* prolactin, respectively (179,180,181). The two larger species can be degraded to the monomeric form by reducing disulfide bonds (182). The proportions of each of these prolactin species vary with physiologic, pathologic, and hormonal stimulation (182,183,184,185). The heterogeneity of secreted forms remains an active area of research. Overall, studies thus far indicate that little prolactin (MW 23,000 daltons) constitutes more than 50% of all combined prolactin production and is most responsive to extrapituitary stimulation or suppression (182,184,185). **Clinical assays for prolactin measure little prolactin, and in all but extremely rare circumstances, these measures are sufficient for assessment of diseases of abnormal pituitary production of the hormone.** Prolactin and its relatives, growth hormone and placental lactogen, do not require glycosylation for most of their primary activities, as is the case with the gonadotropins and TSH. Glycosylated forms are secreted, however, and glycosylation does affect the bioactivity and immunoreactivity of little prolactin (186,187,188,189). It appears that the glycosylated form is the predominant species secreted, but the most potent biologic form appears to be the 23,000-dalton nonglycosylated form of prolactin (188). Prolactin has more than 300 known biological activities, the most recognized of which include those associated with reproduction (lactation, luteal function, and reproductive behavior) and homeostasis (immune responsivity, osmoregulation, and angiogenesis) (190). Despite these many activities, **the only known disorder associated with deficiency of prolactin secretion is inability to lactate.**

To some degree, the physical heterogeneity of prolactin may explain the biologic heterogeneity of this hormone. Although this heterogeneity complicates the physiologic evaluation of prolactin's myriad effects, it is of little importance to the diagnosis and management of hyperprolactinemic states.

In contrast to other anterior pituitary hormones, which are controlled by hypothalamic-releasing factors, prolactin secretion is primarily under inhibitory control mediated by dopamine. **Multiple lines of evidence suggest that dopamine, which is secreted by the tuberoinfundibular dopaminergic neurons into the portal hypophyseal vessels, is the primary prolactin-inhibiting factor.** Dopamine receptors have been found on pituitary lactotrophs (191), and treatment with dopamine or dopamine agonists suppresses prolactin secretion (192,193,194,195,196,197). The dopamine antagonist metoclopramide abolishes the pulsatility of prolactin release and increases serum prolactin levels (193,194,198). **Interference with dopamine transit from the hypothalamus to the pituitary by mass lesions or blockade of the dopamine receptor, which occurs with antipsychotic agents and other medications, increases serum prolactin levels.** Thyrotropin-releasing hormone (TRH), when present at supraphysiologic levels (as in primary hypothyroidism), causes prolactin release, but does not appear to play an important modulatory role in the normal physiologic regulation of prolactin secretion. γ -Aminobutyric acid (GABA) and other neurohormones and neurotransmitters also may function as prolactin-inhibiting factors (see Table 28.7) (199,200,201,202). Several hypothalamic polypeptides that modulate prolactin-releasing activity are listed in Table 28.7. It appears that dopamine and TRH act as primary neurohormones, whereas others (e.g., neuropeptide Y, galanin, and enkephalin) act as modulators. It is likely that under differing physiologic conditions (e.g., pregnancy, lactation, stress, aging), a modulator may become a principal regulator of hormone secretion.

The prolactin receptor is a member of the class 1 cytokine receptor superfamily and is encoded by a gene on chromosome 5 (203). Transcriptional regulation of the prolactin receptor is accomplished through three tissue-specific promoter regions: promoter I for the gonads, promoter II for the liver, and promoter III, a generic promoter that includes the mammary gland (204).

Hyperprolactinemia

Physiologic disturbances, pharmacologic agents, or markedly compromised renal function may cause elevations in prolactin levels, and transient elevations occur with

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acute stress or painful stimuli. The most common cause of elevated prolactin levels is likely pharmacologic; most patients using antipsychotic medications, and many others using agents with antidopaminergic properties, have moderately elevated prolactin levels. Drug-related and physiologic conditions resulting in hyperprolactinemia do not always require direct intervention to normalize prolactin levels.

Table 28.7 Chemical Factors Modulating Prolactin Release and Conditions that Result in Hyperprolactinemia

Inhibitory factors

Dopamine

 γ -Aminobutyric acid

Histidyl-proline diketopiperazine

Pyroglutamic acid

Somatostatin

Stimulatory factors β -Endorphin17 β -Estradiol

Enkephalins

Gonadotropin-releasing hormone

Histamine

Serotonin

Substance P

Thyrotropin-releasing hormone

Vasoactive intestinal peptide

Physiologic conditions

Anesthesia

Empty sella syndrome

Idiopathic

Intercourse

Major surgery and disorders of chest wall (burns, herpes, chest percussion)

Newborns

Nipple stimulation

Pregnancy

Postpartum (nonnursing: days 1-7; nursing: with suckling)

Sleep

Stress

Postpartum

Hypothalamic conditions

Arachnoid cyst

Craniopharyngioma

Cystic glioma

Cysticercosis

Dermoid cyst

Epidermoid cyst

Histiocytosis

Neurotuberculosis

Pineal tumors

Pseudotumor cerebri

Sarcoidosis

Suprasellar cysts

Tuberculosis

Pituitary conditions

Acromegaly

Addison disease

Craniopharyngioma
Cushing syndrome
Hypothyroidism
Histiocytosis
Lymphoid hypophysitis
Metastatic tumors (especially of the lungs and breasts)
Multiple endocrine neoplasia
Nelson syndrome
Pituitary adenoma (microadenoma or macroadenoma)
Post-oral contraception
Sarcoidosis
Thyrotropin-releasing hormone administration
Trauma to stalk
Tuberculosis
Metabolic dysfunction
Ectopic production (hypernephroma, bronchogenic sarcoma)
Hepatic cirrhosis
Renal failure
Starvation refeeding
Drug conditions
α Methyldopa
Antidepressants (<i>amoxapine, imipramine, amitriptyline</i>)
<i>Cimetidine</i>
Dopamine antagonists (<i>phenothiazines, thioxanthenes, butyrophenone, diphenylbutylpiperidine, dibenzoxazepine, dihydroindolone, procainamide, metaclopramide</i>)
Estrogen therapy
Opiates
<i>Reserpine</i>
<i>Sulpiride</i>
<i>Verapamil</i>

Evaluation

Plasma levels of immunoreactive prolactin are 5 to 27 ng/mL throughout the normal menstrual cycle. Samples should not be obtained soon after the patient awakes or after procedures. Prolactin is secreted in a pulsatile fashion with a pulse frequency ranging from about 14 pulses per 24 hours in the late follicular phase to about 9 pulses per 24 hours in the late luteal phase. There also is a diurnal variation, with the lowest levels occurring in midmorning. Levels rise 1 hour after the onset of sleep and continue to rise until peak values are reached between 5:00 and 7:00 AM (205,206). The pulse amplitude of prolactin appears to increase from early to late follicular and luteal phases (207,208,209). Because of the variability of secretion and inherent limitations of radioimmunoassay, an elevated level should always be rechecked. This sample preferably is obtained midmorning and not after a stressful event, previous venipuncture, breast stimulation, or physical examination, all of which transiently increase prolactin levels.

When prolactin levels are found to be elevated, hypothyroidism and medication use should first be ruled out as a cause. Prolactin and TSH determinations are basic evaluations

in infertile women. Infertile men with hypogonadism also should be tested. Likewise, prolactin levels should be measured in the evaluation of amenorrhea, galactorrhea, amenorrhea with galactorrhea, hirsutism with amenorrhea, anovulatory bleeding, and delayed puberty (Fig. 28.5).

Physical Signs

Elevations in prolactin may cause amenorrhea or galactorrhea. Amenorrhea without galactorrhea is associated with hyperprolactinemia in approximately 15% of women (210,211,212). The cessation of normal ovulatory processes resulting from elevated prolactin levels primarily is due to the suppressive effects of prolactin, via hypothalamic mediation, on GnRH pulsatile release (192,210,211,213,214,215,216,217,218,219,220,221). In addition to inducing a hypogonadotropic state, prolactin elevations may secondarily impair the mechanisms of ovulation through a number of actions: causing a reduction in granulosa cell number and FSH binding (222), inhibiting granulosa cell 17β -estradiol production by interfering with FSH action (222,223,224), and causing inadequate luteinization and reduced luteal secretion of progesterone (225,226,227). Other causes of amenorrhea are detailed in Chapter 27.

Although isolated galactorrhea is considered indicative of hyperprolactinemia, prolactin levels are within the normal range in nearly 50% of such patients (228,229,230) (see Fig. 28.5). In such cases, whether because of a prior transient episode of hyperprolactinemia or other unknown factors, the sensitivity of the breast to the lactotrophic stimulus engendered by normal prolactin levels is sufficient to result in galactorrhea. This situation is similar to that observed in breastfeeding mothers in whom milk secretion, once established, continues and even increases despite progressive normalization of prolactin levels. Repeat testing may be helpful in detecting hyperprolactinemia. Approximately one third of women with galactorrhea have normal menses. Conversely, hyperprolactinemia often occurs in the absence of galactorrhea (66%), possibly as a result of inadequate estrogenic or progestational priming of the breast.

In patients with both galactorrhea and amenorrhea (including the syndromes described and named by Forbes, Henneman, Griswold, and Albright in 1951, Argonz and del Castilla in 1953, and Chiari and Frommel in 1985), **approximately two thirds will have hyperprolactinemia; of those, approximately one third will have a pituitary adenoma** (231). In anovulatory women, 3% to 10% of women diagnosed with polycystic ovary disease have coexistent and usually modest hyperprolactinemia (232,233) (Fig. 28.6).

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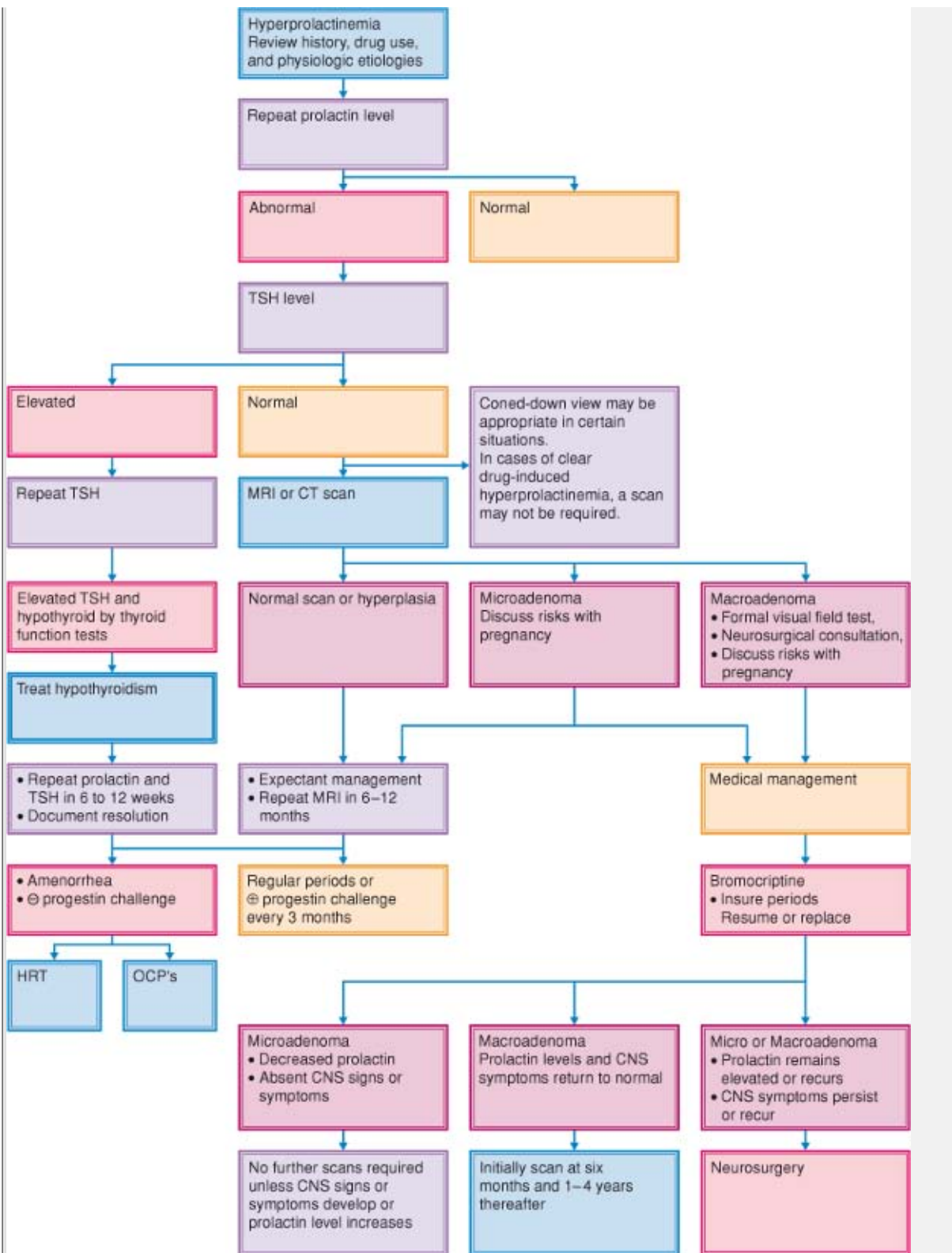


Figure 28.5 Workup for hyperprolactinemia. TSH, thyroid-stimulating hormone; MRI, magnetic resonance imaging; CT, computed tomography; HRT, Hormone Replacement Therapy; OCP's, Oral Contraceptive pills; CNS, central nervous system.

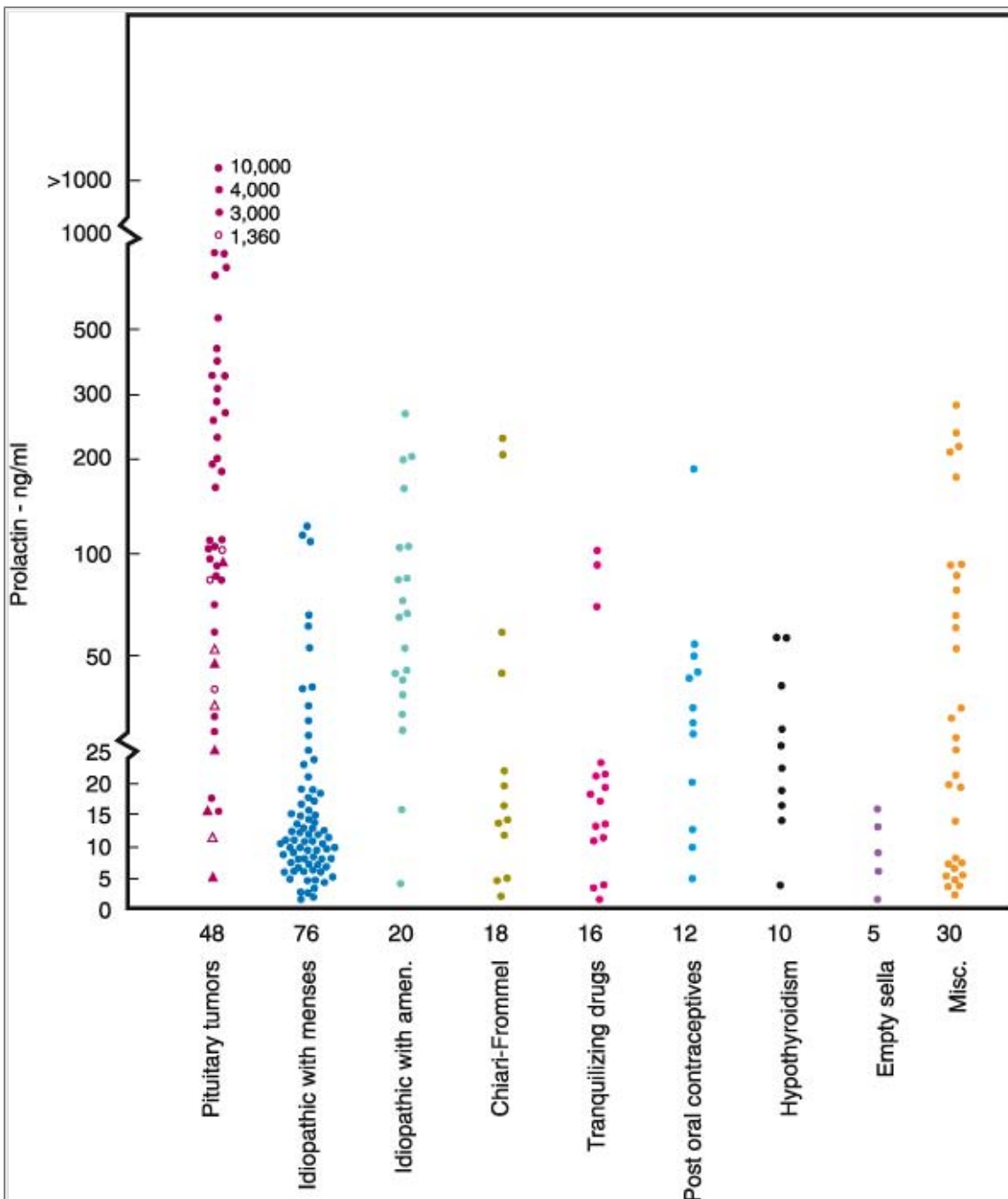


Figure 28.6 Prolactin levels in 235 patients with galactorrhea. Among patients with a tumor, open triangles denote associated acromegaly, and solid circles and solid triangles denote previous radiotherapy or surgical resection, respectively. (From **Kleinberg DL, Noel GL, Frantz AG.** Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 1977;296:589–600.)

Prolactin and TSH levels should be measured in all patients with delayed puberty.

Pituitary abnormalities, including craniopharyngiomas and adenomas, should be considered in all cases of delayed puberty accompanied by low levels of gonadotropins, regardless whether prolactin levels are elevated. When prolactin-secreting pituitary adenomas are present, the condition of multiple endocrine neoplasia type 1 (MEN-1) syndrome (gastrinoma, insulinoma, parathyroid hyperplasia, and pituitary neoplasia) should be considered, although symptoms of pituitary adenoma are rarely the presenting symptom. Patients who have a pituitary adenoma and a family history of multiple adenomas warrant special attention (234). Prolactinomas are noted in approximately 20% of patients with MEN-1. The *MEN-1* gene

suppressor gene. An inactivating mutation results in development of the tumor. It is thought that prolactin-secreting pituitary adenomas that occur in patients with MEN-1 may be more aggressive than sporadic cases (235).

Once an elevated prolactin level is documented and medications or hypothyroidism excluded as the underlying cause, knowledge of neuroanatomy as well as imaging techniques and their interpretation are required for further evaluation (see Chapter 7).

Pituitary hyperprolactinemia is most often caused a microadenoma, and the results of imaging studies usually are normal. These patients can be reassured that the course of their condition generally is benign. Macroadenomas or juxtaseellar lesions are less common and require more complex evaluation and treatment, including surgery, radiation, or both. Levels of TSH should be measured in all patients with hyperprolactinemia (see Fig. 28.5).

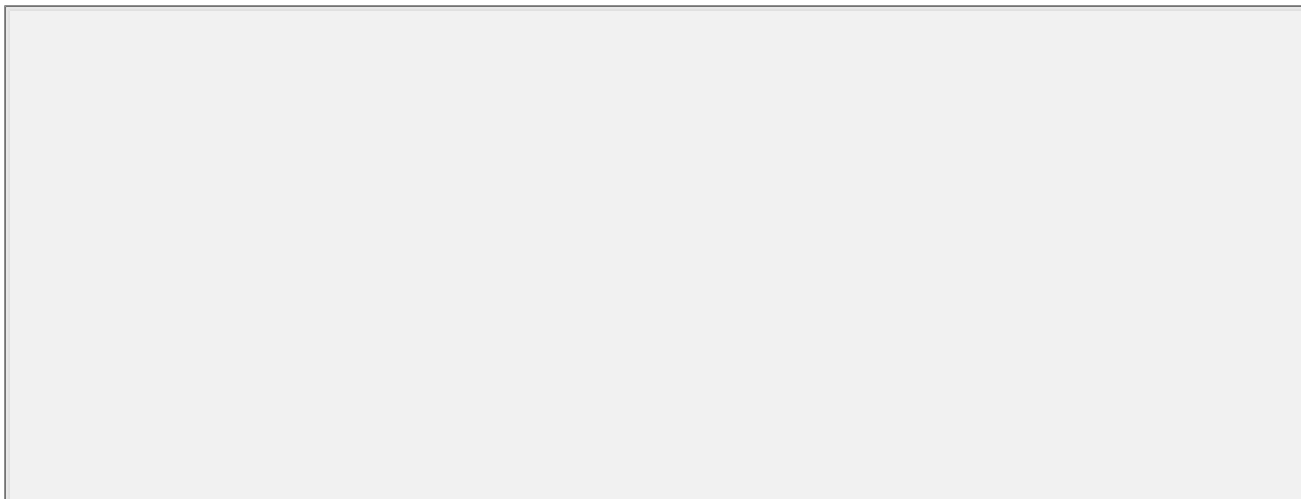
Imaging Techniques

In patients with larger microadenomas and macroadenomas, prolactin levels usually are higher than 100 ng/mL. However, levels lower than 100 ng/mL may be associated with smaller microadenomas, macroadenomas that produce a "stalk section" effect, and suprasellar tumors that may be easily missed on a "coned-down" view of the sella turcica.

Modest elevations of prolactin can, therefore, be associated with microadenomas or macroadenomas, nonlactotroph pituitary tumors, and other central nervous system abnormalities. Imaging of the pituitary gland must be considered in the presence of otherwise unexplained and persistent elevation of prolactin (Table 28.8).

In patients with a clearly identifiable drug-induced or physiologic hyperprolactinemia, imaging is not necessary unless it is accompanied by symptoms suggesting a mass lesion (headache, visual field deficits). **Magnetic resonance imaging of the sella and pituitary gland with gadolinium enhancement appears to provide the best anatomic detail (236) (Fig. 28.7).** The cumulative radiation dose from multiple CT scans may cause cataracts, and the "coned-down" views or tomograms of the sella are very insensitive and likewise expose the patient

to radiation. For patients with hyperprolactinemia who desire future fertility, MRI is indicated to differentiate a pituitary microadenoma from a macroadenoma, as well as to identify other potential sellar or suprasellar masses. Although rare, when pregnancy-related complications of a pituitary adenoma occur, they occur more frequently in the presence of macroadenomas.



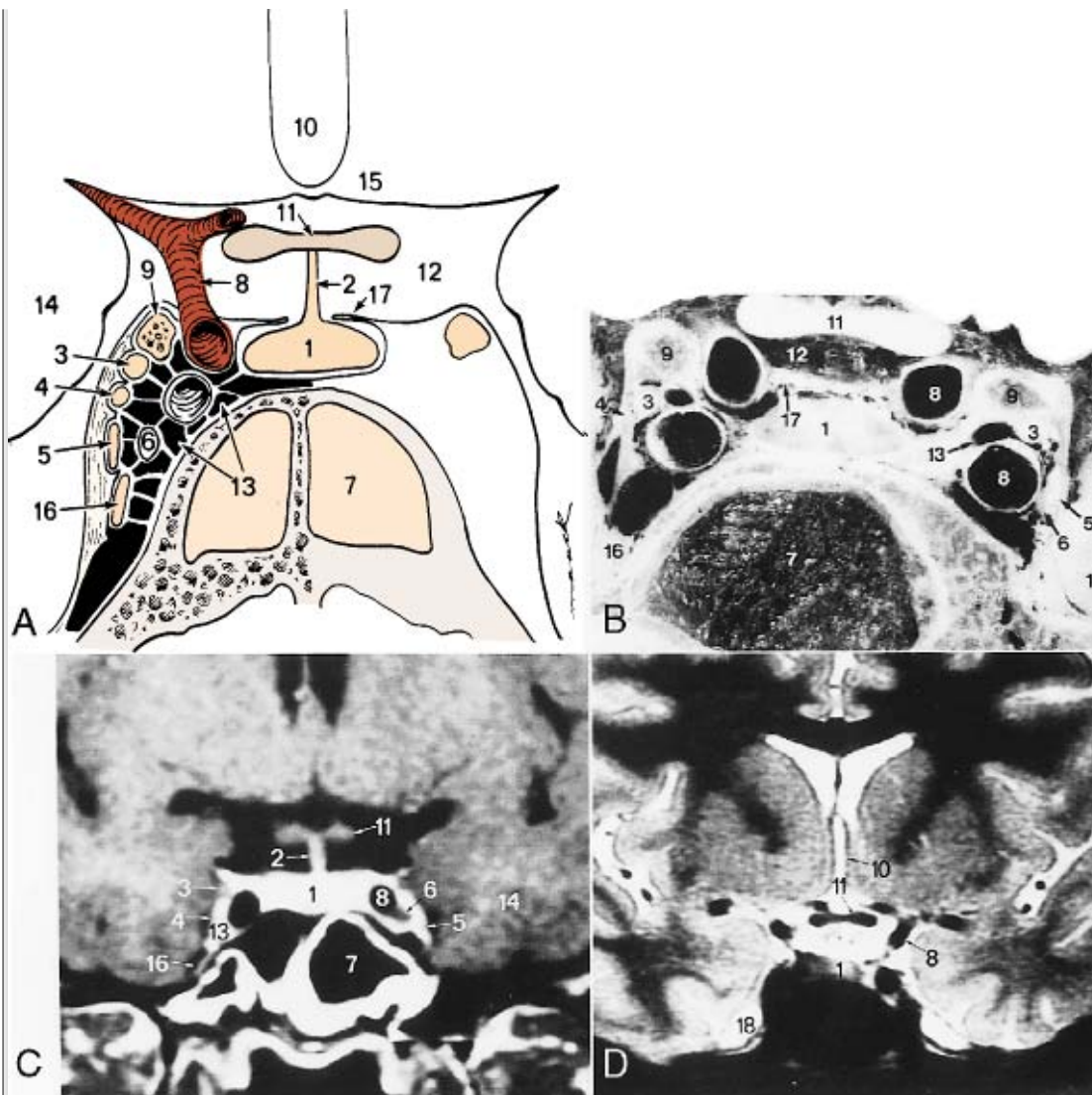


Figure 28.7 Anatomy of the intrasellar region and cavernous sinus by: (A) anatomic diagram, (B) coronal cytomicrosome section, (C) coronal postcontrast T1-weighted magnetic resonance imaging (MRI), and (D) coronal postcontrast T2-weighted MRI. (1, pituitary gland; 2, infundibular stalk; 3, cranial nerve (CN) III; 4, CN IV; 5, CN VI; 6, CN VI; 7, sphenoid sinus; 8, internal carotid artery; 9, anterior clinoid process; 10, third ventricle; 11, optic chiasm; 12, suprasellar cistern; 13, venous spaces of cavernous sinus; 14, temporal lobe; 15, hypothalamus; 16, CN V₂; 17, diaphragma sellae; 18, Meckel's cave.) (Figure kindly provided by Anne G. Osborn, MD).

Table 28.8 Sellar and Suprasellar Tumors and Conditions that May Result in Hyperprolactinemia

Abscess	Lipoma
Aneurysm	Lymphoma
Arachnoid cyst	Meningioma
Cephalocele	Meningitis (bacterial, fungal, granulomatous)
Chloroma (granulocytic sarcoma)	Metastasis
Colloid cyst	Mucocele
Craniopharyngioma	Nasopharyngeal carcinoma
Dermoid	Opticochiasmatic-hypothalamic glioma
Ectopic neurohypophysis	Osteocartilaginous tumor

"Empty" sella	Paracytic cyst
Epidermoid tumor	Pars intermedia cysts
Germinoma	Pituitary adenoma
Hamartoma (tuber cinereum/hypothalamus)	Rathke's cleft cyst
Histiocytosis	Sarcoidosis
Hyperplasia	
Hypophysitis	

In more than 90% of untreated women, microadenomas do not enlarge over a 4- to 6-year period. For that reason, the argument that medical therapy will prevent a microadenoma from growing is false. Additionally, although prolactin levels correlate with tumor size, both elevations and reductions in prolactin levels may occur without any change in tumor size. If prolactin levels increase significantly or central nervous system symptoms (e. g., headache, visual changes) occur, repeat imaging may be indicated.

Hypothalamic Disorders

Dopamine was the first of many substances demonstrated to be produced in the arcuate nucleus. Dopamine-releasing neurons innervate the external zone of the median eminence. When released into the hypophyseal portal system, dopamine inhibits prolactin

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release in the anterior pituitary. Lesions that disrupt dopamine release can result in hyperprolactinemia. Such lesions may arise from the suprasellar area, pituitary gland, and infundibular stalk, as well as from adjacent bone, brain, cranial nerves, dura, leptomeninges, nasopharynx, and vessels. Numerous pathologic entities and physiologic conditions in the hypothalamic-pituitary region can disrupt dopamine release and cause hyperprolactinemia (see Table 28.8).

Pituitary Disorders

Microadenoma

Autopsy series reveal that 25% of the U.S. population has microadenomas, and approximately 40% stain positively for prolactin. Clinically significant pituitary tumors requiring some type of intervention affect only 14 per 100,000 individuals.

In more than one third of women with hyperprolactinemia, a radiologic abnormality consistent with a microadenoma (less than 1 cm) is found. Release of pituitary stem-cell growth inhibition via activation or loss-of-function mutations results in cell cycle dysregulation and is critical to the development of pituitary microadenomas and macroadenomas. Microadenomas are monoclonal in origin. Genetic mutations are thought to release stem-cell growth inhibition and result in autonomous anterior pituitary hormone production, secretion, and cell proliferation. Additional anatomic factors that may contribute to adenoma formation include reduced dopamine concentrations in the hypophyseal portal system and vascular isolation of the tumor, or both. Recently, the heparin-binding secretory transforming (*HST*) gene has been noted in a variety of cancers as well as in prolactinomas (237). **Patients with microadenomas can generally be reassured of a benign course, and many of these lesions gradually regress spontaneously** (238,239).

Both microadenomas and macroadenomas are monoclonal in origin. Pituitary

prolactinomas or lactotrope adenomas are sparsely or densely granulated histologically. The sparsely granulated lactotrope adenomas have trabecular, papillary, or solid patterns. Calcification of these tumors may take the form of a psammoma body or a pituitary stone. Densely granulated lactotrope adenomas are strongly acidophilic tumors and appear to be more aggressive than sparsely granulated lactotrope adenomas. Unusual acidophil stem-cell adenomas can be associated with hyperprolactinemia with some clinical or biochemical evidence of growth hormone excess.

Microadenomas rarely progress to macroadenomas. Six large series of patients with microadenomas reveal that, with no treatment, the risk of progression for microadenoma to a macroadenoma is only 7% (240). Treatments include expectant, medical, or, rarely, surgical therapy. All affected women should be advised to notify their physicians of chronic headaches, visual disturbances (particularly tunnel vision consistent with bitemporal hemianopsia), and extraocular muscle palsies. Formal visual field testing is rarely helpful unless imaging suggests compression of the optic nerves.

Expectant Management

In women who do not desire fertility, expectant management can be used for both microadenomas and hyperprolactinemia in the absence of an adenoma if menstrual function remains intact. Hyperprolactinemia-induced estrogen deficiency, rather than prolactin itself, is the major factor in the development of osteopenia (241).

Therefore, **estrogen replacement with hormone regimens or hormonal contraceptives is indicated for patients with amenorrhea or irregular menses. Patients with drug-induced hyperprolactinemia can also be managed expectantly with attention to the risks of osteoporosis. In the absence of symptoms of pituitary enlargement,** imaging may be repeated in 12 months and, if prolactin levels remain stable, less frequently thereafter to assess further growth of the microadenoma.

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Medical Treatment

Ergot alkaloids are the mainstay of therapy. In 1985, *bromocriptine* was approved for use in the United States to treat hyperprolactinemia caused by a pituitary adenoma. These agents act as strong dopamine agonists, thus decreasing prolactin levels. Effects on prolactin levels occur within hours, and lesion size may decrease within 1 to 2 weeks. *Bromocriptine* decreases prolactin synthesis, DNA synthesis, cell multiplication, and overall size of prolactinomas. Treatment results in normal prolactin blood levels or return of ovulatory menses in 80% to 90% of patients.

Because ergot alkaloids such as *bromocriptine* are excreted via the biliary tree, it should be used with caution in the presence of liver disease. The major adverse effects include nausea, headaches, hypotension, dizziness, fatigue and drowsiness, vomiting, headaches, nasal congestion, and constipation. Many patients tolerate *bromocriptine* **when dose is increased gradually, by 1.25 mg (one half tablet) daily each week until prolactin levels are normal or a dose of 2.5 mg twice daily is reached. A proposed regimen is as follows: one half tablet every evening (1.25 mg) for 1 week, one half tablet morning and evening (1.25 mg) during the second week, one half tablet in the morning (1.25 mg) and a full tablet every evening (2.5 mg) during the third week, and one tablet every morning and every evening during the fourth week and thereafter (2.5 mg twice a day).** The lowest dose that maintains the prolactin level in the normal range is continued (1.25 mg twice daily often is sufficient to normalize prolactin levels in individuals with levels <100 ng/mL). Pharmacokinetic studies show peak serum levels occur 3 hours after an oral

dose, with a nadir at 7 hours. Because little detectable *bromocriptine* remains in the serum by 11 to 14 hours, twice-a-day administration is required. Prolactin levels can be checked soon (6–24 hours) after the last dose is taken.

One rare but notable adverse effect of *bromocriptine* is a **psychotic reaction**. Symptoms include auditory hallucinations, delusional ideas, and changes in mood that quickly resolve with discontinuation of the drug (242). Many investigators report no difference in fibrosis, calcification, prolactin immunoreactivity, or the surgical success in patients pretreated with *bromocriptine* compared with those not receiving *bromocriptine* (240).

An alternative to oral administration is the vaginal administration of *bromocriptine* tablets, which is well tolerated and actually results in increased pharmacokinetic measures (243).

Cabergoline, another ergot alkaloid, has a very long half-life and can be given orally twice per week. Its long duration of action is attributable to slow elimination by pituitary tumor tissue, high affinity binding to pituitary dopamine receptors, and extensive enterohepatic recirculation.

Cabergoline, which appears to be as effective as *bromocriptine* in lowering prolactin levels and in reducing tumor size, has substantially fewer adverse effects than bromocriptine. Very rarely, patients experience nausea and vomiting or dizziness with *cabergoline*; they may be treated with intravaginal *cabergoline*, as with *bromocriptine*. Although *cabergoline* appears to be safe to use during pregnancy, more extensive data regarding the use of *bromocriptine* in pregnancy is available; therefore *bromocriptine* is preferred for pregnant patients. A gradually increasing dosage helps avoid the side effects of nausea, vomiting, and dizziness. *Cabergoline* at 0.25 mg twice per week is usually adequate for hyperprolactinemia with values less than 100 ng/mL. If required to normalize prolactin levels, the dosage can be increased by 0.25 mg per dose on a weekly basis to a maximum of 1 mg twice weekly.

When *bromocriptine* or *cabergoline* cannot be used, other medications such as *pergolide* or *methergoline* may be used. In patients with a microadenoma who are receiving *bromocriptine* therapy, a repeat MRI scan may be performed if indicated 6 to 12 months after prolactin levels are normal. Normal prolactin levels and resumption of menses should not be considered absolute proof of tumor response to treatment. Further MRI scans should be performed if new symptoms appear.

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Discontinuation of *bromocriptine* **therapy after 2 to 3 years may be attempted in a select group of patients in whom normal prolactin levels have been maintained with therapy** (244,245). Discontinuation of *cabergoline* therapy has also been successful in patients treated for 3 to 4 years who have maintained normal prolactin levels (246). In general, recurrence rates are higher for macroadenomas (as compared with microadenomas or hyperprolactinemia without adenoma) after cessation of either bromocriptine or cabergoline, warranting close follow-up with serum prolactin assessment and MRI after cessation of therapy. In patients with macroadenomas, withdrawal of therapy should proceed with caution because tumors may re-expand rapidly.

Macroadenomas

Macroadenomas are pituitary tumors that are larger than 1 cm. *Bromocriptine* is the best initial and potentially long-term treatment option, but transsphenoidal surgery may be required. Evaluation for pituitary hormone deficiencies may be indicated. Symptoms of macroadenoma enlargement include severe headaches, visual field changes and, rarely, diabetes insipidus and blindness.

Medical Treatment

Treatment with *bromocriptine* **decreases prolactin levels and the size of macroadenomas**; nearly one half show a 50% reduction in size, and another one fourth show a 33% reduction after 6 months of therapy. Because tumor regrowth occurs in more than 60% of cases after discontinuation of *bromocriptine* therapy, long-term therapy is usually required.

After stabilization of tumor size is documented, an MRI scan is repeated 6 months later and, if stable, yearly for several years. This examination may be performed earlier if new symptoms develop or if there is no improvement in symptoms. Serum prolactin levels are measured every 6 months. Because tumors may enlarge despite normalized prolactin values, a reevaluation of symptoms at regular intervals (6 months) is prudent. Normalized prolactin levels or resumption of menses should not be taken as absolute proof of tumor response to treatment.

Surgical Intervention

Tumors that are unresponsive to *bromocriptine* **or that cause persistent visual field loss require surgical intervention**. Some neurosurgeons have noted that a short (2-week) preoperative course of *bromocriptine* increases the efficacy of surgery in patients with larger adenomas (243). Unfortunately, despite surgical resection, recurrence of hyperprolactinemia and tumor growth is common. Complications of surgery include cerebral carotid artery injury, diabetes insipidus, meningitis, nasal septal perforation, partial or panhypopituitarism, spinal fluid rhinorrhea, and third nerve palsy. Periodic MRI scanning after surgery is indicated, particularly in patients with recurrent hyperprolactinemia.

Metabolic Dysfunction and Hyperprolactinemia

Occasionally, patients with hypothyroidism exhibit hyperprolactinemia with remarkable pituitary enlargement caused by thyrotroph hyperplasia. Thyroid replacement therapy can reduce pituitary enlargement and normalize prolactin levels (247).

Hyperprolactinemia occurs in 20% to 75% of women with chronic renal failure. Hemodialysis does not lower prolactin levels, but levels become normal with transplantation (248,249,250). Occasionally, women with hyperandrogenemia also have hyperprolactinemia. Elevated prolactin levels may alter adrenal function by enhancing the release of adrenal androgens such as DHEAS (251).

Drug-induced Hyperprolactinemia

Numerous drugs interfere with dopamine secretion and can therefore be responsible for hyperprolactinemia and its attendant symptoms (see Table 28.7). If medication can be discontinued, resolution of hyperprolactinemia is uniformly prompt. If not,

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endocrine management should be directed toward replacing estrogen and normalizing menses for those with disturbed or absent ovulation. Treatment with *dopamine agonists* may be utilized if ovulation is desired and the drug inducing hyperprolactinemia cannot be discontinued.

Use of Estrogen in Hyperprolactinemia

In rodents, pituitary prolactin-secreting adenomas occur with high-dose estrogen administration (252). Elevated levels of estrogen, such as those that occur in pregnancy, are responsible for hypertrophy and hyperplasia of lactotrophic cells and account for the progressive increase in prolactin levels in normal pregnancy. The increase in prolactin during pregnancy is physiologic and reversible, however, and adenomas are not fostered by

the hyperestrogenemia of pregnancy. Pregnancy may even have a favorable influence on pre-existing prolactinomas (253,254). Estrogen administration is not associated with clinical, biochemical, or radiologic evidence of growth of pituitary microadenomas or the progression of idiopathic hyperprolactinemia to the status of an adenoma (255,256,257,258). For these reasons, **estrogen replacement or OC use is appropriate for hypoenestrogenic patients with hyperprolactinemia secondary to microadenoma or hyperplasia.**

Monitoring Pituitary Adenomas During Pregnancy

Prolactin-secreting microadenomas rarely create complications during pregnancy. However, monitoring of patients with serial gross visual field examinations and funduscopic examination is recommended. If persistent headaches, visual field deficits, or visual or funduscopic changes occur, MRI scanning is advisable. **Because serum prolactin levels progressively rise throughout pregnancy, prolactin measurements are rarely of value.**

For those women who experience return of spontaneous ovulation and become pregnant while taking *bromocriptine*, discontinuation of *bromocriptine* is recommended.

This does not, however, preclude subsequent use of *bromocriptine* during the pregnancy to treat symptoms (visual field defects, headaches) that arise from further enlargement of the microadenoma (259,260,261,262). *Bromocriptine* has not exhibited teratogenicity in animals, and observational data do not suggest it is harmful to the pregnancy or the fetus in humans.

Pregnant women with previous transsphenoidal surgery for microadenomas or macroadenomas may be monitored additionally with monthly Goldman perimetry visual field testing. Periodic MRI scanning may be necessary in women with symptoms or visual changes. **Breastfeeding is not contraindicated in the presence of microadenomas or macroadenomas** (259,260,261,262). The use of *bromocriptine* and presumably other dopaminergic agents that may cause blood pressure elevation during the postpartum period is contraindicated (263,264,265,266,267).

Thyroid Disorders

Thyroid disorders are 10 times more common in women than men (268).

Approximately 1% of the female population of the United States will develop overt hypothyroidism. Even before the discovery of the long-acting thyroid stimulator (LATS) in women with Graves disease in 1956, numerous investigations demonstrated a link between these autoimmune thyroid disorders and reproductive physiology and pathology (269).

Thyroid Hormones

Iodide is a critical component of the class of hormones known as thyronines, among which the most important are triiodothyronine and thyroxine (T_3 and T_4). Iodide obtained from dietary sources is actively transported into the thyroid follicular cell for synthesis of these

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hormones. Sodium-iodide symporter (NIS) is a key molecule in thyroid function. It allows the accumulation of iodide from the circulation into the thyrocyte against an electrochemical gradient. Sodium-iodide symporter requires energy that is supplied by Na-K ATPase. Uptake is stimulated by TSH. The enzyme thyroid peroxidase (TPO) then oxidizes iodide near the cell-colloid surface and incorporates it into tyrosyl residues within the thyroglobulin molecule, which results in the formation of monoiodotyrosine (MIT) and

diiodotyrosine (DIT). Triiodothyronine (T_3) and thyroxine (T_4), formed by secondary coupling of MIT and DIT, are also catalyzed by TPO. The membrane-bound, heme-containing oligomer, TPO, is localized in the rough endoplasmic reticulum, Golgi vesicles, lateral and apical vesicles, and on the follicular cell surface. Thyroglobulin, the major protein formed in the thyroid gland, has an iodine content of 0.1% to 1.1% by weight. About 33% of the iodine is present in thyroglobulin in the form of T_3 and T_4 , and the remainder is present in MIT and DIT or found as unbound iodine. Thyroglobulin provides a storage capacity capable of maintaining a euthyroid state for nearly 2 months without the formation of new thyroid hormones. The thyroid antimicrosomal antibodies found in patients with autoimmune thyroid disease are directed against the TPO enzyme (270,271).

Thyroid-stimulating hormone regulates thyroidal iodine metabolism by activation of adenylate cyclase. This facilitates endocytosis as a component of iodide uptake, digestion of thyroglobulin-containing colloid, and the release of thyroid hormones T_4 , T_3 , and reverse T_3 . T_4 is released from the thyroid at 40 to 100 times the concentration of T_3 . The concentration of reverse T_3 , which has no intrinsic thyroid activity, is 30% to 50% of T_3 secretion and 1% of T_4 concentration. Of thyroid hormones released, 70% are bound by circulating thyroid-binding globulin (TBG). Although T_4 is present in the circulating storage pool in the highest concentrations, it has a slow turnover rate (about 7 days). Compared with T_4 , the concentration of T_3 is lower and has a higher turnover rate. Approximately 30% of T_4 is converted to T_3 in the periphery. Reverse T_3 participates in regulation of the conversion of T_4 to T_3 . T_3 is the primary physiologically functional thyroid hormone at the cellular level. T_3 binds the nuclear receptor with 10 times the affinity of T_4 . Thyroid hormone effects on cells include increased oxygen consumption, heat production, and metabolism of fats, proteins, and carbohydrates. Systemically, thyroid hormone activity is responsible for the basal metabolic rate. It balances fuel efficiency with performance, much as a carburetor functions in an engine. Hyperthyroid states result in excessive fuel consumption with marginal performance.

Iodide Metabolism

Normal function of the thyroid gland depends on iodine. The present recommended daily allowance by the U.S. National Research Council is 150 to 300 mg/day. Present daily consumption in the United States averages 200 to 600 mg/day and is largely assured by virtue of addition of iodine to many common foodstuffs. Iodine is usually ingested in the form of iodized salt (100 mg of potassium iodine/kg of salt) (272).

In regions where dietary iodine is insufficient, goitrous hypothyroidism among adults and the consequences of inadequate fetal thyroxine are common (endemic goiter and endemic cretinism). Paradoxically, sufficiency of iodine appears to be associated with the development of autoimmune thyroid disorders (273,274) and reduced remission rates in patients treated for Graves disease (275). Animal studies suggest that iodine stimulates immunoglobulin production by B lymphocytes, activates macrophages, and increases the immunogenic potential of thyroglobulin because of the higher iodide content (276,277,278,279).

Risk Factors for Autoimmune Thyroid Disorders

Environmental factors that have been associated with the occurrence of autoimmune thyroid diseases include pollutants (plasticizers, polychlorinated biphenyls, and coal-processing pollutants) (280,281) and antibodies to *Yersinia enterocolitica* (282).

The female hormonal milieu and its effects on immune surveillance undoubtedly play

a role in the increased risk (10-fold) for women to develop autoimmune thyroid disease.

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The immunoglobulins produced against the thyroid are polyclonal, and the multiple combinations of various antibodies present (stimulating versus blocking, complement fixing, and noncytotoxic) combine to create the clinical spectrum of autoimmune thyroid diseases that may affect reproductive function.

Evaluation

Thyroid Function

Total serum T₄ is measured by radioimmunoassay, and these measurements are indifferent to the fraction of T₄ that is bound to its specific binding protein, TBG. Levels of TBG are variable, and many conditions cause elevations in them (e.g., pregnancy, OC use, estrogen therapy, hepatitis, and genetic abnormalities of TBG). Thus, indirect estimation of the unbound ("free") T₄ or its direct measurement are required for clinical evaluation.

The T₃ resin uptake determines the fractional binding of radiolabeled T₃ that is added to a serum sample in the presence of a resin that competes with TBG for T₃ binding.

The binding capacity of TBG in the sample is inversely proportional to the amount of labeled T₃ bound to the artificial resin. Therefore, a low T₃ resin uptake indicates high TBG T₃ receptor site availability and implies high circulating TBG levels.

The free T₄ index (FTI) is obtained by multiplying the serum T₄ concentration by the T₃ resin uptake percentage, yielding an indirect estimate of the levels of free T₄:

$$\mathbf{T_3 \text{ RU } \% \times T_4 \text{ total} = \text{free } T_4 \text{ index}}$$

A high T₃ resin uptake percentage indicates reduced TBG receptor site availability and high free T₄ index and thus hyperthyroidism, whereas a low T₃ resin uptake percentage is a result of increased TBG receptor site binding and thus hypothyroidism. Equilibrium dialysis and ultrafiltration techniques may be used to determine directly the free T₄. Free T₄ and T₃ may also be determined by radioimmunoassay.

Because levels of TSH are sensitive to excessive or deficient levels of circulating thyroid hormone, and because most disorders of hyperthyroidism and hypothyroidism are related to dysfunction of the thyroid gland, TSH levels are used to screen for these disorders. Current TSH sandwich immunoassays are extremely sensitive and capable of differentiating low-normal from pathologic or iatrogenically subnormal values and elevations. Thus, TSH measurements provide the best way to screen for thyroid dysfunction (283) and accurately predict thyroid hormone dysfunction in about 80% of cases.

Immunologic Abnormalities

Many antigen-antibody reactions affecting the thyroid gland can be detected. A number of recognized thyroid autoantigens are listed in Table 28.9. Antibody production to thyroglobulin obviously depends on a breach in normal immune surveillance (273,274). The incidence of thyroid autoantibodies in various autoimmune thyroid disorders is shown in Table 28.10.

Antibodies to thyroglobulin are restricted to one minor and two major epitopes. Antibodies

are mainly noncomplement-fixing immunoglobulin G (IgG) polyclonal antibodies (275). **Antithyroglobulin antibodies are found in patients with Hashimoto thyroiditis, Graves disease, acute thyroiditis, nontoxic goiter, and thyroid cancer.** They also appear in normal women.

Antithyroid peroxidase antibodies (anti-TPO antibodies), previously referred to as antimicrosomal antibodies, are directed against TPO and are found in Hashimoto thyroiditis,

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Graves disease, and postpartum thyroiditis. The antibodies produced are characteristically cytotoxic, complement-fixing IgG antibodies. Antimicrosomal antibodies correlate with the histologic appearance of lymphocytic thyroiditis (259,260). These antibodies can cause artifacts in the measurement of thyroid hormone levels.

<i>Antigen</i>	<i>Location</i>	<i>Function</i>
Thyroglobulin (Tg)	Thyroid	Thyroid hormone storage
Thyroid peroxidase (TPO) (microsomal antigen)	Thyroid	Transduction of signal from TSH
TSH receptor (TSHR)	Thyroid, lymphocytes, fibroblasts, adipocytes (including retro-orbital)	Transduction of signal from TSH
Na⁺/I⁻ symporter (NIS)	Thyroid, breast, salivary or lacrimal gland, gastric or colonic mucosa, thymus, pancreas	ATP-driven uptake of I ⁻ along with Na ⁺

TSH, thyroid-stimulating hormone; ATP, adenosine triphosphate.

Another group of antibodies important in autoimmune thyroid disease binds the TSH receptor. These antibodies often create the signs and symptoms that lead to an evaluation. Thyroid-stimulating hormone receptor antibodies (TSHR-Ab or TRAb) are pathogenic and capable of activating or blocking TSH receptor functions. These antibodies are detected using two approaches—competitive and functional assays. The competition between antibody and TSH for binding to the TSH receptor is the basis for the measurement of TSH-binding inhibitory immunoglobulin (TBII). The functional assay approach is based on the status of the receptor induced by the antibody-receptor interaction. This functional assay measures the production and accumulation of cAMP, thyroid hormone or thyroglobulin secretion, or iodide uptake in thyroid epithelial cells, or Chinese hamster ovary cells transfected with the human TSH receptor. Whereas the competitive assay does not indicate any functional activity of the antibody, the functional assay identifies whether the antibody is agonistic (thyroid-stimulating antibody [TSAb] or antagonistic TSH stimulation-blocking antibody [TSBAbs or TSHBAbs]). Both types of antibodies may be present in the same patient, and the effect is the algebraic sum of the two levels of activity (agonistic and antagonistic) (Fig. 28.8).

Thyroid-stimulating antibody or thyroid-stimulating immunoglobulin (TSI) activates the TSH receptor (Table 28.11). Long-acting thyroid stimulators are monoclonal or limited polyclonal TSAb, which mimic TSH action. They are quantified by their ability to stimulate human thyroid cell cultures to produce cyclic adenosine monophosphate or to release T₃.

Thyroid-stimulating hormone-binding inhibitory immunoglobulin is detectable in two

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varieties: those that block TSH binding and those that block both pre- and postreceptor processes. Several investigators have detected such blocking antibodies in patients with

primary hypothyroidism who have atrophic thyroid glands (277,278,279). The nomenclature and detection assay of TSH receptor antibodies are listed in Table 28.11.

Table 28.10 Prevalence of Thyroid Autoantibodies and Their Role in Immunopathology

Antibody	General Population	Hypothyroid	
		Autoimmune Thyroiditis	Graves Disease
Antithyroglobulin (anti-Tg)	3%	35%–60%	12%–30%
Antimicrosomal thyroid peroxidase (anti-TPO)	10%–15%	80%–99%	45%–80%
Anti-TSH receptor (anti-TSHR)	1%–2%	6%–60%	70%–100%
Anti-Na ⁺ /I [−] 2symporter (anti-NIS)	0%	25%	20%

TSH, thyroid-stimulating hormone.

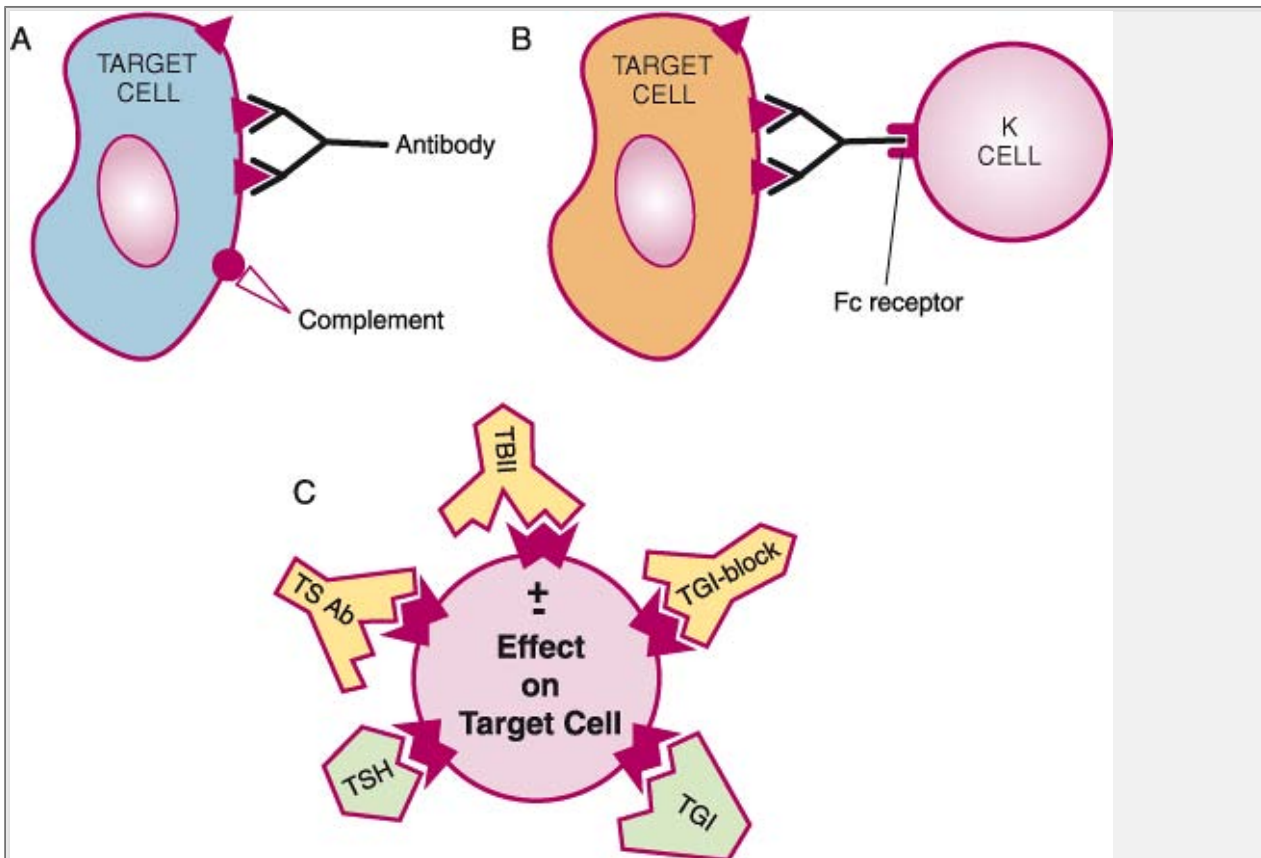


Figure 28.8 Types of autoimmune injury found in Hashimoto thyroiditis. A: Complement-mediated cytotoxicity, which can be abolished by inactivating the complement system. **B:** Antibody-dependent cell-mediated cytotoxicity (ADCC) function through killer T cells, monocytes, and natural killer cells that have immunoglobulin G fragment receptors. **C:** Stimulation or blockade of hormone receptors leading to hyperfunction or hypofunction or growth, depending on the types of immunoglobulins acting on the target cell. (TBII, TSH-binding inhibitor immunoglobulin; TGI, thyroid growth-promoting immunoglobulin; TSAb, thyroid-stimulating antibodies; TSH, thyroid-stimulating hormone.) (From **Coulam CB, Faulk WP, McIntyre JA. Immunologic obstetrics.** New York, NY: Norton Medical Books, 1992:658, with permission.)

Thyroid growth-promoting immunoglobulins (TGI) stimulate growth but not hormone release (250,251,252,253,254,255,256,257,258,259). Their immunologic antagonists are the TGI-blocking antibodies that are capable of inhibiting TSH-mediated growth responses in patients who may have had thyroid damage by immune destruction.

Antibodies to the NIS are prevalent in a number of thyroid conditions. Increased expression of NIS protein and NIS mRNA is found in patients with autonomous thyroid adenomas and Graves disease. They are decreased in Hashimoto thyroiditis, cold nodules, and thyroid carcinoma.

Autoimmune Thyroid Disease

The most common thyroid abnormalities in women, autoimmune thyroid disorders, represent the combined effects of the multiple antibodies produced (284). **The various antigen-antibody reactions result in the wide clinical spectrum of these disorders.**

Transplacental transmission of some of these immunoglobulins may affect thyroid function in the fetus. The presence of autoimmune thyroid disorders, particularly Graves disease, is associated with other autoimmune conditions: Hashimoto thyroiditis, Addison disease, ovarian failure, rheumatoid arthritis, Sjögren syndrome, diabetes mellitus (type I), vitiligo, pernicious anemia, myasthenia gravis, and idiopathic thrombocytopenic purpura. Other factors associated with the development of autoimmune thyroid disorders include low birth weight, iodine excess and deficiency, selenium deficiency, parity, OC use, reproductive age span, fetal microchimerism, stress, seasonal variation, allergy, smoking, radiation damage to the thyroid, and viral and bacterial infections (285).

Table 28.11 Nomenclature of Anti-TSH Receptor Antibodies

<i>Abbreviation</i>	<i>Term</i>	<i>Assay Used</i>	<i>Refers To</i>
LATS	Long-acting thyroid stimulator	<i>In vivo</i> assay of stimulation of mouse thyroid	Original description of serum molecule able to stimulate mouse thyroid; no longer used
TSHR-Ab, TRAb	TSH receptor antibodies	Multiple	All antibodies recognizing the TSH receptor
TBII	TSH-binding inhibitory immunoglobulin	Competitive binding assays with TSH	Antibodies able to compete with TSH for TSH receptor binding irrespective of biologic activity
TSAb	Thyroid-stimulating antibodies	Bioassays of TSH receptor activation	TSH receptor-stimulating antibodies
TSI	Thyroid-stimulating immunoglobulins	As TSAb	Identical to TSAb
TSBAb, TSHBAb	TSH stimulation-blocking antibodies	Competition with TSH in bioassays of TSH receptor activation	Antibodies able to block activation of the TSH receptor by TSH

TSH, thyroid-stimulating hormone.

Certain groups of individuals, including infertile and pregnant women, should undergo an assessment of thyroid function at least once (286). Testing is also recommended for women with atrial fibrillation, hyperemesis gravidarum, and hyperlipidemia. Periodic assessment of thyroid function is indicated in patients who receive amiodarone and lithium.

Epidemiologists recommend that all women with diabetes be tested annually for thyroid dysfunction. Women with type 1 diabetes are three times more likely to experience postpartum thyroid dysfunction, and it is recommended that all pregnant women with diabetes be screened with TSH in the first trimester. Any woman with a history of postpartum thyroiditis should also be offered annual surveillance of thyroid function. Because there is a high prevalence of hypothyroidism in women with Turner and Down syndrome, an annual check of thyroid function is recommended. Periodic TSH screening in mature women is advisable.

Hashimoto Thyroiditis

Hashimoto thyroiditis or chronic lymphocytic thyroiditis, which was first described in 1912, can manifest as hyperthyroidism, hypothyroidism, euthyroid goiter, or diffuse goiter. High levels of antimicrosomal and antithyroglobulin antibody are usually present. Typically, glandular hypertrophy is found, but atrophic forms are also present. The composition of various antibodies (i.e., TBII, causing the atrophic form and congenital hypothyroidism in some neonates, and TGI, causing the goitrous variety) results in varied physical findings.

Three classic types of autoimmune injury are found in Hashimoto thyroiditis: (i) complement-mediated cytotoxicity, (ii) antibody-dependent cell-mediated cytotoxicity, and (iii) stimulation or blockade of hormone receptors, which results in hypo- or hyperfunction or growth (see Fig. 28.8).

The histologic picture of Hashimoto thyroiditis includes cellular hyperplasia, disruption of follicular cells, and infiltration of the gland by lymphocytes, monocytes, and plasma cells. Occasionally, adjacent lymphadenopathy may be noted. Some epithelial cells are enlarged and demonstrate oxyphilic changes in the cytoplasm (Askanazy cells or Hürthle cells, which are not specific to this disorder). The interstitial cells show fibrosis and lymphocytic infiltration. Graves disease and Hashimoto thyroiditis may cause very similar histologic findings manifested by a similar mechanism of action. Nearly all patients with Hashimoto thyroiditis and about two thirds of patients with Graves disease have sera demonstrating antibody-dependent cell-mediated cytotoxicity. Thyroid antibody positivity is detected in 16.8% of white women and in 10.2% of men in the United States (287).

Clinical Characteristics and Diagnosis of Hashimoto Thyroiditis

Most patients with Hashimoto thyroiditis are relatively asymptomatic with painless goiter and hypothyroidism. The goiter can also involve the pyramidal lobe. At later stages of the disease, hypothyroidism can be found without a goiter. Notable manifestations of hypothyroidism include cold intolerance, constipation, carotene deposition in the periorbital region, carpal tunnel syndrome, dry skin, fatigue, hair loss, lethargy, and weight gain. Hashitoxicosis, the hyperthyroid manifestation of Hashimoto thyroiditis, may represent a variant of Graves disease. This form is estimated to occur in 4% to 8% of patients with Hashimoto thyroiditis. These patients often become hypothyroid during the course of treatment.

In many cases, an elevated serum level of TSH is detected during routine screening. Elevated

serum antithyroglobulin and antimicrosomal antibody elevation confirm the diagnosis.

The sedimentation rate may be elevated, depending on the course of the disease at the time of recognition. Other causes of hypothyroidism should be considered as listed in Table 28.12. In light of the annual risk of hypothyroidism (5%) and the potential adverse

effects on the neuropsychological development of the fetus, most clinicians treat women who have elevated serum TSH concentrations and positive thyroid antibody tests, even in the absence of symptoms (subclinical hypothyroidism) (284). If the serum TSH alone is elevated, in the absence of positive thyroid antibody titers, the annual risk for hypothyroidism drops to less than 3% per year.

Table 28.12 Potential Causes of Hypothyroidism

Primary

Congenital absence of thyroid gland

External thyroid gland radiation

Familial disorders and thyroxine synthesis

Hashimoto thyroiditis

Iodine-131 ablation for Graves disease

Ingestion of antithyroid drugs

Iodine deficiency

Idiopathic myxedema (autoimmune)

Surgical removal of thyroid gland

Secondary

Hypothalamic thyrotropin-releasing hormone deficiency

Pituitary or hypothalamic tumors or disease

Treatment

Thyroxine replacement is initiated in patients with symptomatic hypothyroidism, patients who have a goiter that is cosmetically or physically bothersome and are subclinically hypothyroid, and patients who are undergoing fertility therapy and are subclinically hypothyroid. Regression of gland size usually does not occur, but treatment prevents further growth. All pregnant patients with an elevated TSH level should be treated with *levothyroxine*. Treatment does not slow progression of the disease.

Replacement therapy is monitored by TSH determinations at least 6 weeks after a change in dose. *Aluminum hydroxide* (antacids), *cholestyramine*, iron, and *sucralfate* may interfere with absorption. The half-life of *levothyroxine* is nearly 7 days; therefore, nearly 6 weeks of treatment are necessary before the effects of a dose change can be evaluated.

Hypothyroidism appears to be associated with decreased fertility resulting from ovulatory difficulties and possibly with spontaneous abortion (288,289,290,291). A meta-analysis of case-control and longitudinal studies performed since 1990 reveals a possible association between miscarriage and thyroid antibodies with an odds ratio of 2.73 (2.20–3.40, 95% confidence interval). This association may be explained by a heightened autoimmune state affecting the fetal allograft, or, alternatively, a slightly higher age of women with antibodies compared with those without antibodies (0.7 ± 1 year, $P < 0.001$) (292). Studies also suggest that early subclinical hypothyroidism may be associated with menorrhagia (293).

Severe primary hypothyroidism is associated with amenorrhea or anovulation

(294,295). Enhanced sensitivity of the prolactin-secreting cells to TRH and defective dopamine turnover resulting in hyperprolactinemia associated with a deficiency of thyroid hormone are the apparent explanations for the hyperprolactinemia (296,297,298,299). Hyperprolactinemia-induced luteal phase defects also are associated with less severe forms of hypothyroidism (300,301). Replacement therapy appears to reverse the hyperprolactinemia and correct ovulatory defects (302,303).

Combined thyroxine and triiodothyronine therapy is no more effective than thyroxine therapy alone (304). In patients with Hashimoto thyroiditis and subclinical hypothyroidism, a daily dose of 0.025 to 0.075 mg of levothyroxine is usually adequate to normalize TSH values.

Graves Disease

Graves disease, characterized by exophthalmos, goiter, and hyperthyroidism, was first identified as an association of findings in 1835. A heritable specific defect in immunosurveillance by suppressor T lymphocytes is believed to result in the development of a helper T-cell population that reacts to multiple epitopes of the thyrotropin receptor. This activity induces a B-cell-mediated response (301), resulting in the clinical features of Graves disease. The generic TSAbs bind to conformational epitopes in the extracellular domain of the thyrotropin receptor and are detected in the serum of 90% of patients with Graves disease. The epitopes make up discontinuous areas that overlap the thyrotropin binding site. Human leukocyte antigen (HLA) class II antigens DR, DP, DQ, and DS can present antigens to T cells and are expressed on thyroid epithelial cells. Antibodies to the TSH receptor (TSHR-Ab) are produced when this immunogen (TSH receptor) is presented to helper T lymphocytes with the D locus antigens (302).

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The class II antigens are upregulated by chronic stimulation of the TSH receptor, reduction in the iodinating capacity of thyroid tissue, viral transformation, and interferon- α (302,303). The clinical use of *interferon- α* has been associated with autoimmune thyroid disease. Graves disease is a complex autoimmune disorder in which several genetic susceptibility loci and environmental factors are likely to play a role in the development of the disease. Human leukocyte antigen and the CTLA-4 gene region have been established as susceptibility loci; however, the magnitude of their contributions seems to vary among patient populations and study groups. Additional loci are likely to be identified by a combination of genome-wide linkage analyses and allelic association analyses of candidate genes. The rate of concordance for Graves disease is only 20% in monozygotic twins and even lower in dizygotic twins, consistent with a multifactorial inheritance pattern highly influenced by environmental factors. Graves disease is associated with polymorphisms of the cytotoxic T-lymphocyte antigen 4 (*CTLA-4*) gene in several populations. Linkage analysis has identified loci on chromosomes 14q31, 20q11.2, and Xq21 that are associated with susceptibility to Graves disease (305).

Clinical Characteristics and Diagnosis

The classic triad of exophthalmos, goiter, and hyperthyroidism in *Graves disease* is **associated with symptoms of hyperthyroidism: frequent bowel movements, heat intolerance, irritability, nervousness, palpitations or tachycardia, tremor, weight loss, and lower extremity swelling**. Physical findings include lid lag, nontender thyroid enlargement (2 to 4 times normal), onycholysis, palmar erythema, proptosis, staring gaze, and thick skin. A cervical venous bruit and tachycardia are usually noted. The tachycardia does not respond to increased vagal tone produced with a Valsalva maneuver. Severe cases may demonstrate acropachy, chemosis, clubbing, dermopathy, exophthalmos with

ophthalmoplegia, follicular conjunctivitis, pretibial myxedema, and vision loss.

Approximately 40% of patients with new onset of Graves disease and many of those previously treated have elevated T_3 and normal T_4 levels. Therefore, assessment of T_4 , T_3 , and TSH values is indicated. The TSH levels are suppressed, and levels may remain undetectable for some time even after the initiation of treatment. This assessment is useful in evaluating medical treatment and prognosis, and anticipating fetal complications such as neonatal thyrotoxicosis. Autonomously functioning, benign thyroid neoplasms that exhibit a similar clinical picture include toxic adenomas and toxic multinodular goiter. Very rare conditions causing thyrotoxicosis include hCG-secreting choriocarcinoma, TSH-secreting pituitary adenomas, and struma ovarii. Factitious ingestion of thyroxine or desiccated thyroid should be considered in patients with eating disorders. Other potential causes of hyperthyroidism are listed in Table 28.13. Smoking appears to be an independent risk factor for relapse after medical therapy and should be considered when planning treatment.

Treatment

Iodine-131 Ablation

Treatment of women with hyperthyroidism of an autoimmune origin presents unique challenges to the physician who must consider the patient's needs and her reproductive plans. Because the drugs used to treat this disorder have potentially harmful effects on the fetus, special attention must be given to the use of contraception and the potential for pregnancy.

A single dose of radioactive iodine-131 (^{131}I) is an effective cure in about 80% of cases and is the most commonly used definitive treatment in nonpregnant women. Any woman of childbearing age should be tested for pregnancy before undergoing diagnostic or therapeutic administration of ^{131}I . Ablation of a second-trimester fetal thyroid gland and congenital hypothyroidism (cretinism) as a result of treatment during the first trimester have been reported (306,307).

Nuclear medicine professionals

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provide expertise in the administration of the radioactive isotope, and suppressive medical treatment is provided for 6 to 12 weeks after administration of ^{131}I . Medical therapy is the main component of therapy even when radioactive ^{131}I or surgery is eventually planned. Postablative hypothyroidism develops in 50% of patients within the first year after ^{131}I therapy and in more than 2% of patients per year thereafter.

Table 28.13 Potential Causes of Hyperthyroidism

Factitious hyperthyroidism
Graves disease
Metastatic follicular cancer
Pituitary hyperthyroidism
Postpartum thyroiditis
Silent hyperthyroidism (low radioiodine uptake)
Struma ovarii
Subacute thyroiditis
Toxic multinodular goiter
Toxic nodule

Tumors secreting human chorionic gonadotropin (molar pregnancy, choriocarcinoma)

A higher rate of miscarriage has been noted in women treated with ^{131}I therapy in the year preceding therapy, but there has been no reported increase in the rate of stillbirths, preterm birth, low birth weight, congenital malformation, or death after therapy (308). Many thyroidologists and nuclear medicine specialists ascribe the higher rates of miscarriage to unrecognized post ^{131}I induced hypothyroidism and are now more willing to allow pregnancy earlier than 1 year after therapy if patients receive replacement therapy with *levothyroxine*.

Thyroid-stimulating Receptor Antibody in Graves Disease

The level of TSHR–Ab (TBII) grossly parallels the degree of hyperthyroidism as assessed by the serum levels of thyroid hormones and total thyroid volume. Studies suggest that the combination of a small goiter volume (<40 mL) and a low TBII level (<30 units/L) results in a 45% chance of remission during the 5 years after completion of a 12- to 24-month course of antithyroid drug therapy (309). In contrast, the overall rate of relapse exceeded 70% in patients with a large goiter volume (>70 mL) and a higher TBII level (>30 units/L). Thus, the subgroup of patients with larger goiters and higher TBII levels had less than a 10% chance to remain in remission in the 5 years after treatment. Although it is not necessary for the diagnosis of Graves disease, except in some cases of multinodular goiter, a TSHR–Ab measurement may be a useful marker of disease severity. Used in combination with other clinical factors, it may contribute to initial decisions regarding treatment. See Table 28.11 for a review of the nomenclature and assay methods for TSHR–Ab.

Measurements of TSHR–Ab (TBII) during treatment with antithyroid drugs also are predictive of subsequent outcome. In one series, 73% of TBII–negative patients had remission compared with only 28% of TBII–positive patients who had achieved remission after 12 months of antithyroid drug therapy (310). Furthermore, the duration of a course of antithyroid drug therapy can be modified according to the TSHR–Ab status. In patients whose TSHR–Ab status became negative and antithyroid drug therapy was discontinued, the relapse rate was 41% compared with a rate of 92% for those patients who remained TSHR–Ab positive (311). Regardless of the rapidity of the disappearance of TSHR–Ab, it does seem that antithyroid drug therapy should be maintained for 9 to 12 months to minimize the

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risk of relapse. TSHR–Ab status also appears to determine, in an inverse relationship, the reduction in thyroid volume after radioactive iodine therapy.

Recently, a second generation assay has been developed for assessment of TSHR–Ab using recombinant human TSH receptor (312). This new assay has nearly 100% sensitivity and specificity in the diagnosis of Graves disease. Its utility in monitoring treatment is being evaluated. Many patients with Graves disease have or will develop antineutrophil cytoplasmic antibodies (ANCA), but the significance of this finding is still being studied.

Antithyroid Drugs

Antithyroid drugs of the thioamide class include *propylthiouracil* (PTU) and *methimazole*. Low doses of either agent block the secondary coupling reactions that form T_3 and T_4 from MIT and DIT. At higher doses, they also block iodination of tyrosyl residues in thyroglobulin. *Propylthiouracil* additionally blocks the peripheral conversion of T_4 to T_3 . Approximately one third of patients treated by this approach alone go into remission and become euthyroid (309).

Propylthiouracil causes a reduction of hyperthyroid symptoms at a dose of 100 mg taken every 8 hours over 1 month. Adequate control of thyrotoxic symptoms may require considerably higher doses. *Propylthiouracil* blocks the intrathyroid synthesis of T_3 and the peripheral conversion of T_4 to T_3 but does not cross the placenta as easily as *methimazole*; therefore, it is the drug of choice during pregnancy. Drug efficacy is monitored weekly by evaluation of appetite, emotional lability, insomnia, and tremor. A general rule is to lower the dosage by 50% when thyroid function returns to normal, which frequently correlates with the return to a normal heart rate and, subsequently, normalization of TSH levels. Thyroxine is usually the first value to become normal.

Pruritus affects 3% to 5% of treated patients. Serious adverse reactions include agranulocytosis (occurring 1–2 months after therapy in 0.02%) and a generalized drug eruption accompanied by arthralgia, fever, and sore throat. A complete blood count determination is performed if the patient develops an upper respiratory tract infection. If adverse reactions occur, *methimazole* may be used.

***Methimazole* (10 mg) is given every 8 to 24 hours. Its dosage is reduced in a manner similar to that used with *PTU*. It is not the drug of choice in pregnant women because it does not block peripheral conversion and crosses the placenta more readily than *PTU*.** Its use in pregnancy is associated in some instances with the development of characteristic skin lesions in the fetus, aplasia cutis congenita. It does, however, have fewer adverse reactions, a longer dosing interval, and a lower cost than *PTU*; therefore, it is most often prescribed in nonpregnant women.

Other medical therapies include *iodide* and *lithium*, both of which reduce thyroid hormone release and inhibit the organification of iodine. *Iodide* also leads to the secondary coupling of T_3 and T_4 . These medications are rarely used in women of reproductive age because of their risks to the fetal thyroid and to fetal development (*iodine* causes congenital goiter; *lithium* causes Ebstein's anomaly).

Surgery

A subtotal thyroidectomy is less commonly used primarily but is used routinely if medical treatment fails or if a patient is hypersensitive to medical therapy. Surgery is the most rapid and consistent method of achieving a euthyroid state in Graves disease that avoids the possible long-term risks of radioactive iodine. Children, young women, pregnant women, and patients with coexistent thyroid nodules are potential candidates for thyroidectomy. It is felt to be the treatment of choice for a patient with significant Graves ophthalmology. Patients should be rendered euthyroid before a thyroidectomy. The risks of surgery include postoperative hypoparathyroidism, recurrent laryngeal nerve paralysis, routine anesthetic and surgical risks, hypothyroidism, and failure to relieve thyrotoxicosis.

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β -Blockers

Propranolol is occasionally used before surgery in patients who prove to be hypersensitive to other medical therapy. It provides relief of symptoms while awaiting a reduction in T_4 caused by *PTU* or *methimazole*.

Thyroid Storm

In severe hypothyroidism, physiologic stress—including childbirth, systemic infection, or surgery

—may provoke a life-threatening spectrum of symptoms. These include diarrhea, vomiting, and fever, with associated dehydration, as well as altered mental status that may proceed to coma. Patients with poorly controlled hyperthyroidism are most susceptible. Beta-blocker agents, glucocorticoids, *PTU* (the action of which includes inhibition T_4 - T_3 conversion), and iodides are key elements of therapy.

Hyperthyroidism in Gestational Trophoblastic Disease and Hyperemesis Gravidarum

Because of the weak TSH-like activity of hCG, conditions with high levels of hCG, such as molar pregnancy, may be associated with biochemical and clinical hyperthyroidism. Symptoms regress with removal of the abnormal trophoblastic tissue and resolution of elevated levels of hCG. In a similar fashion, when hyperemesis gravidarum is associated with high levels of hCG, mild biochemical and clinical features of hyperthyroidism may be seen (313,314). Gestational trophoblastic disease is reviewed in Chapter 37.

Thyroid Function in Pregnancy

High levels of hCG at the end of the first trimester are sufficient to contribute to the thyrotropic effects of TSH, and TSH levels may show transient depression as a result of this phenomenon. Thyroid hormone requirements in pregnancy increase moderately. Patients depending on replacement thyroid hormone require monitoring to determine the need for increases in thyroid hormone replacement (estimated at 30%) commencing in the first weeks of pregnancy. Evidence suggests that optimal fetal and infant neurodevelopmental outcomes may require careful titration of replacement thyroxine that meets the frequently increased requirements of pregnancy (315,316).

Reproductive Effects of Hyperthyroidism

High levels of TSAb in women with Graves disease have been associated with fetal-neonatal hyperthyroidism (317,318). Despite both the inhibition and elevation of gonadotropins seen in thyrotoxicosis (319), most women remain ovulatory and fertile (320). Severe thyrotoxicosis can result in weight loss, menstrual cycle irregularities, and amenorrhea. An increased risk of spontaneous abortion is noted in women with thyrotoxicosis. An increased incidence of congenital anomalies, particularly aplasia cutis, occurs in the offspring of women treated with *methimazole* (321).

Autoimmune hyperthyroid Graves disease may improve spontaneously, in which case antithyroid drug therapy may be reduced or stopped. Nevertheless, TSHR-Ab production may persist for several years after radical radioactive iodine therapy or surgical treatment for hyperthyroid Graves disease. In this circumstance, there is a risk of exposing a fetus to TSHR-Ab. Fetal-neonatal hyperthyroidism is observed in 2% to 10% of pregnancies occurring in mothers with a current or previous diagnosis of Graves disease, secondary to the transplacental passage of maternal TSHR-Ab. This is a serious condition with a 16% neonatal mortality rate as well as a risk of intrauterine fetal death, stillbirth, and skeletal developmental abnormalities, such as craniosynostosis. Caution against overtreatment with antithyroid medication is also warranted as these medications may cross the placenta in sufficient quantities to induce fetal goiter. Guidelines for TSHR-Ab testing during pregnancy in women with previously treated Graves disease are found in Table 28.14. Fetal goiters and the associated fetal hypo- or hyperthyroid status have been diagnosed accurately in mothers with Graves disease using a combination of fetal ultrasonography of the thyroid with Doppler, fetal heart rate monitoring, bone maturation, and maternal TSHR-

Table 28.14 Guidelines for TSHR–Ab Testing During Pregnancy with Previously Treated Graves Disease

1. In the woman with antecedent Graves disease in remission after ATD treatment, the risk for fetal–neonatal hyperthyroidism is negligible, and systematic measurement of TSHR–Ab is not necessary. Thyroid function should be evaluated during pregnancy to detect an unlikely but possible recurrence. In that case, TSHR–Ab assay is mandatory.

2. In the woman with antecedent Graves disease previously treated with radioiodine or thyroidectomy and regardless of the current thyroid status (euthyroidism with or without thyroxine substitution), TSHR–Ab should be measured early in pregnancy to evaluate the risk for fetal hyperthyroidism. If the TSHR–Ab level is high, careful monitoring of the fetus is mandatory for the early detection of signs of thyroid overstimulation (tachycardia, impaired growth rate, oligohydramnios, goiter). Cardiac echography and measurement of circulatory velocity may be confirmatory. Ultrasonographic measurements of the fetal thyroid have been defined from 20 weeks gestational age but require a well–trained operator, and thyroid visibility may be hindered because of fetal head position. Color Doppler ultrasonography is helpful in evaluating thyroid hypervascularization. Because of the potential risks of fetal–neonatal hyperthyroid cardiac insufficiency and the inability to measure the degree of hyperthyroidism in the mother because of previous thyroid ablation, it may be appropriate to consider direct diagnosis in the fetus. Fetal blood sampling through cordocentesis is feasible as early as 25 to 27 weeks gestation with less than 1% adverse effects (fetal bleeding, bradycardia, infection, spontaneous abortion, *in utero* death) when performed by experienced clinicians. ATD administration to the mother may be considered to treat the fetal hyperthyroidism.

3. In the woman with concurrent hyperthyroid Graves disease, regardless of whether it has preceded the onset of pregnancy, ATD treatment should be monitored and adjusted to keep free T₄ in the high–normal range to prevent fetal hypothyroidism. TSHR–Ab should be measured at the beginning of the last trimester, especially if the required ATD dosage is high. If the TSHR–Ab assay is negative or the level low, fetal–neonatal hyperthyroidism is rare. If antibody levels are high (TBII ≥ 40 U/L or TSAb ≥ 300%), evaluation of the fetus for hyperthyroidism is required. In this condition, there is usually a fair correlation between maternal and fetal thyroid function such that monitoring the ATD dosage according to the mother's thyroid status is appropriate for the fetus. In some cases in which a high dose of ATD (>300 mg/d of propylthiouracil [PTU] or >20 mg/d of methimazole) is necessary, there is a risk of goitrous hypothyroidism in the fetus, which might be indistinguishable from goitrous Graves disease. The correct diagnosis relies on the assay of fetal thyroid hormones and TSH, which allows for optimal treatment.

4. In any woman who has previously given birth to a newborn with hyperthyroidism, a TSHR–Ab assay should be performed early in the course of pregnancy.

TSHR–Ab, thyroid–stimulating hormone receptor antibodies; ATD, autoimmune thyroid disease; T₄, thyroxine; TBII, TSH–binding inhibitory immunoglobulin; TSAb, thyroid–stimulating antibody.

Postpartum Thyroid Dysfunction

This clinical entity is much more common than recognized; it is often difficult to diagnose, because its symptoms appear 1 to 8 months postpartum and often are confused with postpartum depression and difficulties adjusting to the demands of the neonate and infant. Following are criteria for the diagnosis of postpartum thyroiditis: (i) no history of thyroid hormonal abnormalities either before or during pregnancy, (ii) documented abnormal TSH level (either depressed or elevated) during the first year postpartum, and (iii) absence of a positive TSH-receptor antibody titer (Graves disease) or a toxic nodule. An incidence of approximately 5% has been documented (323). A number of studies now describe clinical and biochemical evidence of postpartum thyroid dysfunction in 5% to 10% of new mothers (324). These women have a 25% chance of becoming permanently hypothyroid.

Histologically, lymphocytic infiltration and inflammation are found. Antimicrosomal antibodies are also present in this disorder (325,326). Women who are at greatest risk of developing this disorder are those with a personal or family history of the disorder, those with an autoimmune thyroid disorder, or those with an autoimmune disease.

Clinical Characteristics and Diagnosis

Postpartum thyroiditis usually begins with a transient hyperthyroid phase between 6 weeks and 6 months postpartum followed by a hypothyroid phase. However, only one fourth of the cases follow this classic clinical picture, whereas more than one third

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have either hyperthyroidism or hypothyroidism alone. Individuals with type 1 diabetes are 3 times more likely to develop postpartum thyroiditis, and women with a history of postpartum thyroiditis in a previous pregnancy have nearly a 70% chance of recurrence in a subsequent pregnancy. Numerous case reports demonstrate a possible association between postpartum thyroiditis and other autoimmune disorders. Postpartum thyroiditis appears to be caused by the combination of a rebounding immune system in the postpartum state and the presence of thyroid autoantibodies. Although psychotic episodes are rare, postpartum thyroid dysfunction should be considered in all women with postpartum psychosis. The thyrotoxic phase may be subclinical and overlooked, particularly in areas where iodine intake is low (327). Unlike patients with Graves disease, those with the hyperthyroidism caused by postpartum thyroiditis have a low level of radioactive isotope uptake.

The absence of thyroid tenderness, pain, fever, elevated sedimentation rate, and leukocytosis helps to rule out subacute thyroiditis (de Quervain thyroiditis). Evaluation of TSH, T_4 , T_3 , T_3 resin uptake, and antimicrosomal antibody titer confirm the diagnosis.

Treatment

Most patients are diagnosed during the hypothyroid phase and require 6 to 12 months of T_4 replacement if they are symptomatic. **Because approximately 10% to 30% of women develop permanent hypothyroidism, TSH should be evaluated following discontinuation of replacement therapy.**

Rarely, patients are diagnosed during the hyperthyroid phase (328). Antithyroid medications are not routinely used for these women. *Propranolol* may be used for relief of symptoms. Approximately two thirds of these patients return to a euthyroid state, and one third return to a hypothyroid state.

Antithyroid Antibodies and Disorders of Reproduction

Women who have antithyroid autoantibodies before and after conception appear to be at an increased risk for spontaneous abortion (329,330). Nonorgan-specific antibody production and pregnancy loss are documented in cases of antiphospholipid abnormalities (331). The concurrent presence of organ-specific thyroid antibodies and nonorgan-specific autoantibody production is not uncommon (331,332,333). In cases of recurrent pregnancy loss, thyroid autoantibodies may serve as peripheral markers of abnormal T-cell function and further implicate an immune component as the cause of reproductive failure (334). The clinical implications of these findings in the management of patients with recurrent pregnancy loss is not known. Recurrent pregnancy loss is covered in Chapter 31.

Thyroid Nodules

Thyroid nodules are a common finding on physical examination and are demonstrated by ultrasonography in more than 50% of patients (335). Occasionally such nodules are functional, and clinical and laboratory evaluation should be applied to distinguish these nodules from nonfunctional nodules, which are occasionally malignant. For nonfunctional "cold" nodules, fine-needle biopsy and aspiration are required to rule out malignancy. In the case of indeterminate aspirates, 2% to 20% are malignant; therefore, surgical biopsy often is indicated (336).

Gonadal Dysgenesis and Down Syndrome

Patients with ***gonadal dysgenesis (Turner syndrome***, and other forms of hypergonadotropic hypogonadism associated with abnormalities of the second sex chromosome) exhibit a high prevalence of autoimmune thyroid disorders. Approximately 50% of adult patients with Turner syndrome have antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG) autoantibodies. Of these patients, approximately 30% will develop subclinical or clinical hypothyroidism. The disorder is indistinguishable from Hashimoto thyroiditis. A susceptibility locus for Graves disease is noted on chromosome X (337).

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Down syndrome, caused by an extra chromosome 21, is characterized by an atypical body habitus, mental retardation, cardiac malformations, an increased risk of leukemia, and a reduced life expectancy. The extra chromosome is almost always of maternal origin. Autoimmune thyroid disorders are more common in patients with Down syndrome than in the general population. The gene for autoimmune polyglandular syndrome I (*APECED*) has been mapped to chromosome 21 and is thought to be a transcription factor involved in immune regulation (AIRE). This gene may play a role in the development of autoimmune thyroid disease in these patients (338). Hashimoto thyroiditis is the most common type of thyroid disease in individuals with Down syndrome. Hypothyroidism develops in as many as 50% of patients older than age 40 with Down syndrome. These clinical syndromes and other evidence suggest part of the genetic susceptibility to Hashimoto thyroiditis may reside on chromosomes X and 21.

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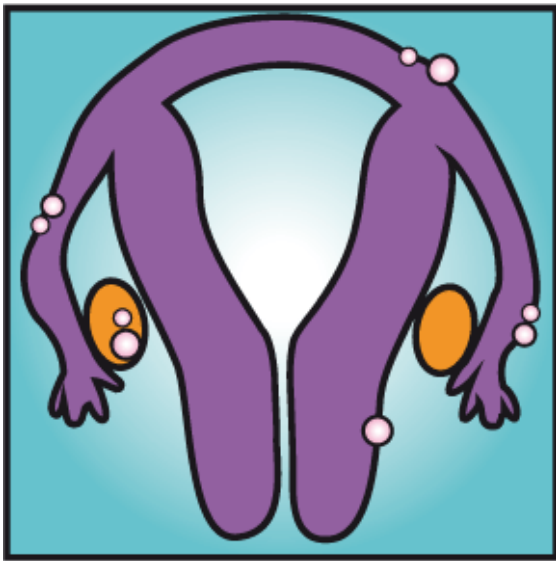
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Endometriosis

Thomas M. D'Hooghe

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- Endometriosis is diagnosed by visual inspection of the pelvis during laparoscopy, ideally with histological confirmation; positive histology confirms the diagnosis, but negative histology does not exclude it.
- Severe or deeply infiltrating endometriosis should be managed in a facility with the necessary expertise to provide treatment in a multidisciplinary context, including advanced laparoscopic surgery and laparotomy.
- Systems currently available for the classification of endometriosis are subjective and correlate poorly with pain symptoms but may be of value in determining the prognosis and management of infertility.
- Suppression of ovarian function for 6 months reduces pain associated with endometriosis. Hormonal drugs are equally effective in reducing pain but have differing side effects and cost.
- Ablation of endometriotic lesions with laparoscopic uterine nerve ablation (LUNA) in

minimal-to-moderate disease reduces pain associated with endometriosis; however, because LUNA used alone has no effect on dysmenorrhea associated with endometriosis, there is no evidence that LUNA is a necessary component of treatment.

- Ablation of endometriotic lesions plus adhesiolysis in minimal-to-mild endometriosis is more effective than diagnostic laparoscopy alone in improving fertility. Suppression of ovarian function is not effective in improving fertility in patients with endometriosis.

Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterus. The most frequent sites of implantation are the pelvic viscera and the peritoneum. Endometriosis varies in appearance from a few minimal lesions on otherwise intact pelvic organs to massive ovarian endometriotic cysts that distort tubo-ovarian anatomy and extensive adhesions often involving bowel, bladder, and ureter. It is estimated to occur in 7% of reproductive-age women in the United States and often is associated

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with pelvic pain and infertility. Considerable progress has been made in understanding the pathogenesis, spontaneous evolution, diagnosis, and treatment of endometriosis.

Etiology

Although signs and symptoms of endometriosis have been described since the 1800s, its widespread occurrence was acknowledged only during the 20th century. Endometriosis is an estrogen-dependent disease. Three theories have been proposed to explain the histogenesis of endometriosis:

- Ectopic transplantation of endometrial tissue.
- Coelomic metaplasia.
- The induction theory.

No single theory can account for the location of endometriosis in all cases.

Transplantation Theory

The transplantation theory, originally proposed by Sampson in the mid-1920s, is based on the assumption that endometriosis is caused by the seeding or implantation of endometrial cells by transtubal regurgitation during menstruation (1). Substantial clinical and experimental data support this hypothesis (2,3). Retrograde menstruation occurs in 70% to 90% of women (4,5), and it may be more common in women with endometriosis than in those without the disease (5). The presence of endometrial cells in the peritoneal fluid, indicating retrograde menstruation, has been reported in 59% to 79% of women during menses or in the early follicular phase (6,7), and these cells can be cultured *in vitro* (7). The presence of endometrial cells in the dialysate of women undergoing peritoneal dialysis during menses supports the theory of retrograde menstruation (8). Endometriosis is most often found in dependent portions of the pelvis—the ovaries, the anterior and posterior cul-de-sac, the uterosacral ligaments, the posterior uterus, and

the posterior broad ligaments (9).

Endometrium obtained during menses can grow when injected beneath abdominal skin or into the pelvic cavity of animals (10,11). Endometriosis has been found in 50% of Rhesus monkeys after surgical transposition of the cervix to allow intra-abdominal menstruation (12).

Increased retrograde menstruation by obstruction of the outflow of menstrual fluid from the uterus is associated with a higher incidence of endometriosis in women (13,14) and in baboons (15). Women with shorter intervals between menstruation and longer duration of menses are more likely to have retrograde menstruation and are at higher risk for endometriosis (16).

Ovarian endometriosis may be caused by either retrograde menstruation or by lymphatic flow from the uterus to the ovary (17). Extrapelvic endometriosis, although rare (1%–2%), potentially may result from vascular or lymphatic dissemination of endometrial cells to many gynecologic (vulva, vagina, cervix) and nongynecologic sites. The latter include bowel (appendix, rectum, sigmoid colon, small intestine, hernia sacs), lungs and pleural cavity, skin (episiotomy or other surgical scars, inguinal region, extremities, umbilicus), lymph glands, nerves, and brain (18).

Coelomic Metaplasia

The transformation (metaplasia) of coelomic epithelium into endometrial tissue has been proposed as a mechanism for the origin of endometriosis. Previously this theory had not been supported by either strong clinical or experimental data. One study evaluating structural and cell surface antigen expression in the rete ovarii and epoöphoron reported little commonality between endometriosis and ovarian

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surface epithelium, suggesting that serosal metaplasia is unlikely in the ovary (19). In contrast, the results of another study involving the genetic induction of endometriosis in mice suggest that ovarian endometriotic lesions may arise directly from the ovarian surface epithelium through a metaplastic differentiation process induced by activation of an oncogenic *K-ras* allele (20).

Induction Theory

The induction theory is, in principle, an extension of the coelomic metaplasia theory. It proposes that an endogenous (undefined) biochemical factor can induce undifferentiated peritoneal cells to develop into endometrial tissue. This theory has been supported by experiments in rabbits (21,22) but has not been substantiated in women and primates.

Genetic Factors

There is increasing evidence to suggest that endometriosis is at least partially a genetic disease. Recent findings that support this association include evidence of familial clustering in humans and in rhesus monkeys, a founder effect detected in the Icelandic population, concordance in monozygotic twins, a similar age at onset of symptoms in affected nontwin sisters, a 6- to 9-times increased prevalence of endometriosis among first-degree relatives of women compared with the general population, and a 15% prevalence of magnetic resonance imaging (MRI) findings suggestive of endometriosis in the first-degree relatives of women with stage III–IV disease based on the classification of the American Society of Reproductive Medicine (23). **The induction of humanlike endometriosis by genetic activation of an oncogenic *K-ras* allele lends further support to the genetic basis of this disorder (20).**

Population Studies

The risk of endometriosis is 7 times greater if a first-degree relative has been affected by endometriosis (24). Because no specific Mendelian inheritance pattern has been identified, multifactorial inheritance has been postulated. A relative risk for endometriosis of 7.2 has been found in mothers and sisters, and a 75% (6 of 8) incidence has been noted in homozygotic twins of patients with endometriosis (25). In another study of twins, 51% of the variance of the latent liability to endometriosis may be attributable to additive genetic influences (26). Other investigators reported that 14 monozygotic twin pairs were concordant for endometriosis, and 2 pairs were discordant (27). Of these twin pairs, 9 had moderate to severe endometriosis.

A relationship has been shown between endometriosis and systematic lupus erythematosus (28), dysplastic nevi, and a history of melanoma in women of reproductive age (29). Endometriosis also is linked to the presence of individual human leukocyte antigens (30,31,32).

Mutations

In women with endometriosis, no mutations were found in the *TP53* and *RASK* genes (33). No significant differences were observed in *N314D* (galactose-1-phosphate uridylyl transferase) mutation frequency between women with endometriosis (18%) and controls (17%) (34).

Steroid Receptor Genetics

An association of estrogen receptor gene polymorphisms (two-allele and multiallele polymorphism) with endometriosis has been reported (35). Furthermore, various exon-deleted progesterone-receptor messenger RNAs (mRNAs) have been documented in human endometrium and ovarian endometriosis (36).

Aneuploidy

Epithelial cells of endometriotic cysts are monoclonal on the basis of phosphoglycerate kinase gene methylation, but normal endometrial glands are monoclonal (37,38). In a

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comparison of endometriotic tissue with normal tissue from the endometrium flow, cytometric DNA analysis failed to show aneuploidy (39). However, more recent studies using comparative genomic hybridization (40) or multicolor *in situ* hybridization (41) showed aneuploidy for chromosomes 11, 16, and 17 (41), increased heterogeneity of chromosome 17 aneuploidy (42), and losses of 1p and 22q (50%), 5p (33%), 6q (27%), 70 (22%), 9q (22%), and 16 (22%) of 18 selected endometriotic tissues (40).

Loss of Heterozygosity

Microsatellite DNA assays reveal an allelic imbalance (loss of heterozygosity) in *p16 (Ink4)*, *GALT*, *p53*, and *APOA2* loci in patients with endometriosis, even in stage II of endometriosis (43). Another report (38) found in 28% of endometriotic lesions a loss of heterozygosity at one or more sites: chromosomes 9p (18%), 11q (18%), and 22q (15%).

Immunologic Factors and Inflammation

Although retrograde menstruation appears to be a common event in women, not all and Inflammation women who have retrograde menstruation develop endometriosis.

The immune system may be altered in women with endometriosis, and it has been hypothesized that the disease may develop as a result of reduced immunologic clearance of viable endometrial cells from the pelvic cavity

(44,45). Endometriosis can be caused by decreased clearance of peritoneal fluid endometrial cells resulting from reduced natural killer (NK) cell activity or decreased macrophage activity (46). Decreased cell-mediated cytotoxicity toward autologous endometrial cells has been associated with endometriosis (46,47,48,49,50). However, these studies used techniques that have considerable variability in target cells and methods (51,52). Whether NK cell activity is lower in patients who have endometriosis than in those without endometriosis is controversial. Some reports demonstrate reduced NK activity (53,54,55,56,57), whereas others have found no increase in NK activity, even in women with moderate to severe disease (48,49,50,58). There also is great variability in NK cell activity among normal individuals that may be related to variables such as smoking, drug use, and exercise (51).

In contrast, endometriosis can also be considered a condition of immunologic tolerance, as opposed to ectopic endometrium, which essentially is self-tissue (44). It can be questioned why viable endometrial cells in the peritoneal fluid would be a target for NK cells or macrophages. Autotransplantation of blood vessels, muscles, skin grafts, and other tissues is known to be extremely successful (47,48,49). Furthermore, there is no *in vitro* evidence that peritoneal fluid macrophages actually attack and perform phagocytosis of viable peritoneal fluid endometrial cells. High-dose immunosuppression can slightly increase the progression of spontaneous endometriosis in baboons (59). There is no clinical evidence, however, that the prevalence of endometriosis is increased in immunosuppressed patients. The fact that women with kidney transplants, who undergo chronic immunosuppression, are not known to have increased infertility problems can be considered indirect evidence that these patients do not develop extensive endometriosis.

Substantial evidence suggests that endometriosis is associated with a state of subclinical peritoneal inflammation, marked by an increased peritoneal fluid volume, increased peritoneal fluid white blood cell concentration (especially macrophages with increased activation status), and increased inflammatory cytokines, growth factors, and angiogenesis-promoting substances. It has been reported in baboons that subclinical peritoneal inflammation occurs both during menstruation and after intrapelvic injection of endometrium (57). A higher basal activation status of peritoneal macrophages in women with endometriosis may impair fertility by reducing sperm motility, increasing sperm phagocytosis, or interfering with fertilization (60,61), possibly by increased secretion of cytokines such as tumor necrosis factor- α (TNF- α) (62,63,64). Tumor necrosis factor also may facilitate the pelvic implantation of ectopic endometrium (63,64). The adherence of human endometrial stromal cells to mesothelial cells *in vitro* has been increased by the

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pretreatment of mesothelial cells with physiologic doses of TNF- α (65). Macrophages or other cells may promote the growth of endometrial cells (66,67,68) by secretion of growth and angiogenetic factors such as epidermal growth factor (EGF) (65), macrophage-derived growth factor (MDGF) (69), fibronectin (70), and adhesion molecules such as integrins (71). After attachment of endometrial cells to the peritoneum, subsequent invasion and growth appear to be regulated by matrix metalloproteinases (MMP) and their tissue inhibitors (72,73).

There is increasing evidence that local inflammation and secretion of prostaglandins (PG) is related to differences in endometrial aromatase activity between women with and without endometriosis. Expression of aromatase cytochrome P450 protein and mRNA was present in human endometriotic implants but not in normal endometrium, suggesting that ectopic endometrium produces estrogens, which may be involved in the tissue growth

interacting with the estrogen receptor (74). Inactivation of 17β -estradiol has been reported to be impaired in endometriotic tissues because of deficient expression of 17β -hydroxysteroid dehydrogenase type 2, which is normally expressed in eutopic endometrium in response to progesterone (75). The inappropriate aromatase expression in endometriosis lesions can be stimulated by prostaglandin E^2 (PGE^2). This reaction leads to local production of E^2 , which also stimulates PGE^2 production, resulting in a positive-feedback system between local inflammation and estrogen-driven local growth of ectopic endometrium (76).

The subclinical pelvic inflammatory status associated with endometriosis is also reflected in the systemic circulation. Increased concentrations of C-reactive protein, serum amyloid A (SAA), TNF- α , membrane cofactor protein-1, interleukin-6, interleukin-8 and chemokine (C-C motif) receptor 1 (CCR1) have been observed in peripheral blood samples of patients with endometriosis when compared with controls (77). This observation can be the basis for the development of noninvasive diagnostic tests.

Environmental Factors and Dioxin

There is an increasing awareness of potential links between reproductive health, infertility, and environmental pollution. Attention has been directed to the potential role of dioxins in the pathogenesis of endometriosis, but the issue remains controversial. A recent meta-analysis concluded that currently there is insufficient evidence in women or in nonhuman primates that endometriosis is caused by dioxin exposure (78).

Human Data

A 1976 explosion of a factory in Seveso (Italy) resulted in the highest levels of dioxin exposure recorded in humans (79), but so far no data have been published. The Seveso Women's Health Study will correlate prospective individual data on exposure to dioxin with reproductive endpoints such as the incidence of endometriosis, infertility, and decreased sperm quality. Thus far, one case-control study has failed to show in the general population an association between endometriosis and exposure to polychlorinated biphenyl and chlorinated pesticides during adulthood. No differences in mean plasma concentrations of 14 polychlorinated biphenyl and 11 chlorinated pesticides were found between women with and those without endometriosis (80). Genetic mechanisms may play a role in dioxin exposure and the development of endometriosis. Transcripts of the *CYP1A1* gene, a dioxin-induced gene, have been reported to be significantly higher (9 times higher) in endometriotic tissues than in eutopic endometrium (81). Other investigators have reported a similar expression of arylhydrocarbon receptor and dioxin-related genes (using semiquantitative reverse transcriptase polymerase chain reaction) in the endometrium from women with or without endometriosis (82). In Japanese women, no association was found between endometriosis prevalence or severity and polymorphisms for arylhydrocarbon receptor repressor, arylhydrocarbon (x2) receptor, and arylhydrocarbon nuclear translocator or *CYP1A1* genes (83). Based on these data, there is insufficient

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evidence supporting the association between endometriosis and dioxin exposure in humans.

Primates

An initial retrospective case-control study reported that the prevalence of endometriosis was not statistically different (Fisher exact test, $p=0.08$) between monkeys chronically exposed to dioxin during 4 years (11 of 14, 79%) and in nonexposed animals (2 of 6, 33%) after a period of 10 years. However, a positive correlation was found between the severity of endometriosis

and dioxin dose, serum levels of dioxin, and dioxinlike chemicals (84,85). Two prospective studies have evaluated the association between dioxin exposure and development of endometriosis in Rhesus monkeys. In the most recent study (86), monkeys exposed over 12 months to low-dose dioxin (0.71 ng/kg/day) had endometriosis implants with smaller maximal and minimal diameters and similar survival rate when compared with endometriotic lesions in unexposed controls, suggesting no effect of dioxin on endometriosis. However, after 12 months of exposure to high-dose dioxin (17.86 ng/kg/day), larger diameters and a higher survival rate of endometriosis implants were observed in exposed Rhesus monkeys compared with nonexposed controls. The second randomized controlled study performed in 80 Rhesus monkeys compared those with no treatment with those treated with 0, 5, 20, 40, and 80 µg of *Aroclor* (1,254/kg/day) for 6 years. Endometriosis occurred in 37% of controls and in 25% of treated monkeys as determined by laparoscopy and necropsy data (87). No association was observed between endometriosis severity and polychlorinated biphenyl exposure. These data question the importance of dioxin exposure, except at high doses, in the development of endometriosis in primates.

Rodents

Continuous exposure to 2,3,7,8-tetrachlorodibenzo-P-dioxin inhibited the growth of surgically induced endometriosis in ovariectomized mice treated with high-dose estradiol. No correlation was observed between the dose of dioxin and survival of endometrial implants, adhesions, and serum E₂ levels (88). In ovariectomized mice induced with endometriosis, similar stimulating effects of estrone and 4-chlorodiphenyl ether (4-CDE) were observed on survival rates of endometriotic mice, suggesting an estrogenlike effect of 4-CDE (89). Potential mechanisms mediating dioxin action to promote endometriosis in rodents are complex and probably different in rats and mice, not to mention women. The mouse appears to be a better model to elucidate these mechanisms (90,91), but both models have important limitations.

Future Research

The study of endometriosis is compounded by the need to exclude other causes and to assess symptoms within the context of the pelvic condition (i.e., the presence or absence of pathology). The pathogenesis of endometriosis, the pathophysiology of related infertility, and the spontaneous evolution of endometriosis are being investigated. At the time of diagnosis, most patients with endometriosis have had the disease for an unknown period, making it difficult to initiate any clinical experiments that would determine definitely the etiology or progression of the disease (3). Because endometriosis occurs naturally only in women and primates and invasive experiments cannot be performed easily, it is difficult to undertake properly controlled studies. Thus, there is a need for the development of a good animal model with spontaneous endometriosis.

The main advantage of the rat and rabbit animal models used to study endometriosis is their low cost relative to primates. The disadvantages are numerous, however. Rodents lack a menstrual cycle comparable to that of primates and are not subject to spontaneous endometriosis. Whereas the rat ovulates spontaneously, it has a shorter luteal phase than humans. The reproductive pattern of the rabbit lacks a luteal phase. There is a wide phylogenetic gap between these two species and the human. In both rodent models, the

type of lesions appear to be quite different from the variety of pigmented and nonpigmented lesions observed in women (92,93,94).

Primates, conversely, are phylogenetically close to humans, have a comparable menstrual cycle, are afflicted with spontaneous endometriosis, and when induced with endometriosis, develop macroscopic lesions that are similar to those found in human disease (12,95,96,97,98,99). Although the great apes are closest to humans in many anatomic and physiologic aspects of reproduction, they are not practical models for study; therefore, Rhesus and cynomolgus monkeys have been used. Baboons may be a better choice for study because they are continuous breeders, are phylogenetically very close to humans, and have similar reproductive anatomy and physiology with regard to menstrual cycle characteristics and regularity, embryo implantation, and fetal development (95). In addition, spontaneous endometriosis in the baboon has been found to be both minimal and disseminated, similar to the different stages of endometriosis in women (95,100,101). Experimental endometriosis can be successfully induced by the intrapelvic injection of menstrual endometrium (11). In recent years, the baboon has been established in about 30 peer-reviewed articles as an excellent model for endometriosis research (102). Future research on the pathogenesis of endometriosis, using the baboon model, should focus on the early interactions between endometrial and peritoneal cells in the pelvic cavity at the time of menstruation. Proteomic and genomic approaches can detect potential differences between eutopic endometrium and myometrium in women with and without endometriosis. Immunomodulatory drugs inhibiting pelvic inflammation associated with endometriosis may offer new approaches to medical treatment in the future (103).

Prevalence

Endometriosis is predominantly found in women of reproductive age but has been reported in adolescents and in postmenopausal women receiving hormonal replacement (104). It is found in women of all ethnic and social groups. **In women with pelvic pain or infertility, a high prevalence of endometriosis (from a low of 20% to a high of 90%) has been reported (2,105).** **In asymptomatic women undergoing tubal ligation (women of proven fertility), the prevalence of endometriosis ranges from 3% to 43% (5,106,107,108,109,110).** This great variation in the reported prevalence may be explained by several factors. First, it may vary with the diagnostic method used: laparoscopy, the operation of choice for diagnosis, is generally accepted to be a better method than laparotomy for diagnosing minimal to mild endometriosis. Second, minimal or mild endometriosis may be more thoroughly evaluated in a symptomatic patient being given general anesthesia than in an asymptomatic patient during tubal sterilization. Third, the experience of the surgeon is important because there is a wide variation in the appearance of subtle endometriosis implants, cysts, and adhesions. Most studies that evaluate the prevalence of endometriosis in women of reproductive age lack histologic confirmation (5,106,107,110,111,112,113,114,115).

Diagnosis

Clinical Presentation

Endometriosis should be suspected in women with subfertility, dysmenorrhea, dyspareunia, or chronic pelvic pain. However, these symptoms can also be associated with other diseases. Endometriosis may be asymptomatic, even in some women with more advanced disease (ovarian or deeply invasive rectovaginal endometriosis).

Risk factors for endometriosis include short cycle length (116), heavier menstruation, and longer flow duration (16,117), probably related to a higher incidence of retrograde

menstruation. Patient height and weight are positively and negatively, respectively, associated with the risk of endometriosis (118).

Endometriosis can be associated with significant gastrointestinal symptoms (pain, nausea, vomiting, early satiety, bloating and distention, altered bowel habits).

A characteristic motility change (ampulla of Vater–duodenal spasm, a seizure equivalent of the enteric nervous system), along with bacterial overgrowth, has been documented in most women with the disease (119). Women of reproductive age with endometriosis are not osteopenic (120).

The average delay between onset of pain symptoms and surgically confirmed endometriosis is quite long: ± 8 years in the United Kingdom and ± 9 to 12 years in the United States (121). Similar durations have been observed in Scandinavia (122) and in Brazil (123). A delay in diagnosis of endometriosis of 6 and 3 years in women with pain and women with infertility, respectively, has been reported. Over the past two decades, there has been a steady decrease in the delay in diagnosis and a decline in the prevalence of advanced endometriosis at first diagnosis (124). Concurrently, patient awareness of endometriosis has increased. For many patients, quality of life is affected by pain, emotional impact of subfertility, anger about disease recurrence, and uncertainty about the future regarding repeated surgeries or long-term medical therapy and its side effects. Therefore, **endometriosis should be perceived as a chronic disease, at least in a subset of highly symptomatic women, and quality-of-life issues should be evaluated using reliable and valid questionnaires** (125).

Pain

In adult women, dysmenorrhea may be especially suggestive of endometriosis if it begins after years of pain-free menses. Dysmenorrhea often starts before the onset of menstrual bleeding and continues throughout the menstrual period. In adolescents, the pain may be present after menarche without an interval of pain-free menses. The distribution of pain is variable but most often is bilateral.

Local symptoms can arise from rectal, ureteral, and bladder involvement, and lower back pain can occur. **Most studies have failed to detect a correlation between the degree of pelvic pain and the severity of endometriosis** (108). Some women with extensive disease have no pain, whereas others with only minimal disease may experience severe pelvic pain. Severe pelvic pain and dyspareunia may be associated with deep infiltrating subperitoneal endometriosis (105,115,126). The character of pelvic pain is related to the anatomic location of deeply infiltrating endometriotic lesions (127).

Possible mechanisms causing pain in patients with endometriosis include local peritoneal inflammation, deep infiltration with tissue damage, adhesion formation, fibrotic thickening, and collection of shed menstrual blood in endometriotic implants, resulting in painful traction with the physiologic movement of tissues (115,128).

In rectovaginal endometriotic nodules, a close histologic relationship has been observed between nerves and endometriotic foci and between nerves and the fibrotic component of the nodule (129).

Subfertility

An association between endometriosis and subfertility is generally accepted, but most of the studies suggesting this link have been based on retrospective or cross-sectional analysis

(130). **When endometriosis is moderate or severe, involving the ovaries and causing adhesions that block tubo-ovarian motility and ovum pickup, it is associated with subfertility** (131). This effect has also been shown in primates, including cynomolgus monkeys and baboons (98,132). Although numerous mechanisms (ovulatory dysfunction, luteal insufficiency, luteinized unruptured follicle syndrome, recurrent abortion,

altered immunity, and intraperitoneal inflammation) have been proposed (133), the association between fertility and minimal or mild endometriosis remains controversial (130,131).

Infertility

Based on the number of asymptomatic women who are found to have endometriosis during tubal ligation, it would appear that the prevalence of endometriosis is not necessarily higher in infertile than in fertile women with endometriosis (5). **In fertile women, endometriosis has been reported to be minimal or mild in 80% and moderate or severe in 20%** (5,106,107,108,109,110).

In women with mild disease, some studies have reported a lower spontaneous monthly fecundity rate (MFR), which is the total number of pregnancies divided by the number of months of pregnancy exposure (i.e., 5%–11% compared with 25% in a normally fertile population) (133). Other studies using artificial insemination with donor semen have reported that the MFR in women with minimal and mild endometriosis is either reduced (4%) or normal (20%) (134,135,136,137). Fertility is not reduced in baboons with spontaneous minimal endometriosis (132,138). In one study, the fecundity rate (probability of becoming pregnant in the first 36 weeks after laparoscopy and carrying the pregnancy to 20 weeks or more) was 18% in infertile women with minimal to mild endometriosis and 23.7% in women with unexplained infertility (no significant difference). None of these women had been surgically treated for endometriosis during the diagnostic laparoscopy. However, 10% of women in each group had been treated with intrauterine insemination, *in vitro* fertilization (IVF), or cystectomy–myomectomy (139). **It remains unclear whether the mere presence of peritoneal endometriosis directly correlates with infertility.**

Spontaneous Abortion

A possible association between endometriosis and spontaneous abortion has been suggested in mostly uncontrolled or retrospective studies. Some controlled studies evaluating the association between endometriosis and spontaneous abortion have important methodologic shortcomings: heterogeneity between cases and controls, analysis of the abortion rate before the diagnosis of endometriosis, and selection bias of study and control groups (140,141,142). **Based on controlled prospective studies, there is no evidence that endometriosis is associated with (recurrent) pregnancy loss (143), or that medical or surgical treatment of endometriosis reduces the spontaneous abortion rate** (144,145).

Endocrinologic Abnormalities

Endometriosis has been associated with anovulation, abnormal follicular development with impaired follicle growth, reduced circulating E₂ levels during the preovulatory phase, disturbed luteinizing hormone (LH) surge patterns, premenstrual spotting, the luteinized unruptured follicle syndrome, and galactorrhea and hyperprolactinemia (146). Increased incidence and recurrence of the luteinized unruptured follicle syndrome has been reported in baboons with mild endometriosis, but not in primates with minimal endometriosis or a

normal pelvis (147). Luteal insufficiency with reduced circulating E₂ and progesterone levels, out-of-phase endometrial biopsies, and aberrant integrin expression has been reported in the endometrium of women with endometriosis by some researchers (146,148), but these findings have not been confirmed by other investigators (149). Therefore, no convincing data exist to conclude that the incidence of these endocrinologic abnormalities is increased in women who have endometriosis.

Extrapelvic Endometriosis

Extrapelvic endometriosis, although often asymptomatic, should be suspected when symptoms of pain or a palpable mass occur outside the pelvis in a cyclic pattern. Endometriosis involving the intestinal tract (especially colon and rectum) is the most common site of extrapelvic disease and may cause abdominal and back pain, abdominal distention, cyclic rectal bleeding, constipation, and obstruction. Ureteral involvement can

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lead to obstruction and result in cyclic pain, dysuria, and hematuria. Pulmonary endometriosis can manifest as pneumothorax, hemothorax, or hemoptysis during menses. Umbilical endometriosis should be suspected when a patient has a palpable mass and cyclic pain in the umbilical area (18).

Clinical Examination

In many women with endometriosis, no abnormality is detected during the clinical examination. The vulva, vagina, and cervix should be inspected for any signs of endometriosis, although the occurrence of endometriosis in these areas is rare (e.g., episiotomy scar). Other possible signs of endometriosis include uterosacral or cul-de-sac nodularity, lateral or cervical displacement caused by uterosacral scarring (150), painful swelling of the rectovaginal septum, and unilateral ovarian (cystic) enlargement. In more advanced disease, the uterus is often in fixed retroversion, and the mobility of the ovaries and fallopian tubes is reduced. Evidence of deeply infiltrative endometriosis (deeper than 5 mm under the peritoneum) in the rectovaginal septum with cul-de-sac obliteration or cystic ovarian endometriosis should be suspected by clinical documentation of uterosacral nodularities during menses, especially if CA125 serum levels are higher than 35 IU/mL (151,152,153).

The clinical examination may have false-negative results. Therefore, the diagnosis of endometriosis should be confirmed by biopsy of suspicious lesions that are obtained laparoscopically.

Imaging and Endometriosis

The presence of filling defects (presence of hypertrophic or polypoid endometrium) detected by hysterosalpingography (154) has a significant positive correlation with endometriosis. The positive predictive value of this finding is 84% and negative predictive value is 75%.

Gynecologic transvaginal (155) or transrectal ultrasonography (156) is an important diagnostic tool (157) in the assessment of ovarian endometriotic cysts (differentiation from other adnexal masses) and of rectovaginal endometriosis (sensitivity, 97%; specificity, 96%).

Other imaging techniques, including computed tomography (CT) and MRI, can be used to provide additional and confirmatory information, but they cannot be used for primary diagnosis (158,159). These techniques are more costly than ultrasonography, and their added value is not clear.

CA125

There is no blood test available for the diagnosis of endometriosis. Levels of CA125, a marker found on derivatives of the coelomic epithelium and common to most nonmucinous epithelial ovarian carcinomas, have been found to be significantly higher in women with moderate or severe endometriosis and normal in women with minimal or mild disease (160,161). During menstruation, an increase in CA125 levels has been shown in women with and without endometriosis (162,163,164,165,166). Other studies have not found an increase during menses (167,168) or have found an increase only with moderate to severe endometriosis (169,170). The levels of CA125 vary widely, not only in patients without endometriosis (8–22 U/mL in the nonmenstrual phase) but also in those with minimal to mild endometriosis (14–31 U/mL in the nonmenstrual phase) and in those with moderate to severe disease (13–95 U/mL in the nonmenstrual phase). **Compared with laparoscopy, measurement of serum CA125 levels has no value as a diagnostic tool** (171).

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The reason CA125 levels are increased in moderate to severe endometriosis is unclear. It has been hypothesized that endometriosis lesions contain a greater amount of CA125 than normal endometrium and that the associated inflammation could lead to an increased shedding of CA125 (161).

The specificity of CA125 has been reported to be higher than 80% in most studies. This high level of specificity is achieved in selected women with infertility or pain who are known to be at risk for endometriosis. The low level of sensitivity of CA125 (20%–50% in most studies) poses limitations for the clinical use of this test for diagnosis of endometriosis. Theoretically, the sensitivity might increase during the menstrual period, when the increase in CA125 levels is more pronounced in women who have endometriosis. However, studies using cutoff levels of 35 U/mL (169,170) or 85 U/mL (172) have not found a significant improvement in sensitivity. A sensitivity of 66% was found when CA125 was determined during both the follicular phase and the menstrual phase in each patient and when the ratio of menstrual versus follicular values (≥ 1.5) was used instead of one CA125 level (170). More recent studies reported that the value of CA125 in diagnosis of endometriosis is limited but higher for moderate to severe disease, especially if serum CA125 concentrations are measured during the midfollicular phase (171,173).

Serial CA125 determinations may be useful to predict the recurrence of endometriosis after therapy (174,175). CA125 levels decrease after combined medical and surgical therapy or during medical treatment of endometriosis with *danazol*, gonadotropin-releasing hormone (GnRH) analogues, or *gestrinone*, but not with *medroxyprogesterone acetate* (MPA) or placebo (176,177,178). Levels of CA125 have been reported to increase to pretreatment levels as early as 3, 4, or 6 months after the cessation of therapy with *danazol*, GnRH analogs, or *gestrinone* (166,177,178,179,180,181). Posttreatment increases in CA125 levels have been reported to correlate with endometriosis recurrence (165,175,182). However, other studies have not substantiated a correlation between posttreatment CA125 levels and disease recurrence (176,179,183).

Laparoscopic Findings

Unless disease is visible in the vagina or elsewhere, laparoscopy is the standard technique for visual inspection of the pelvis and establishment of a definitive diagnosis (159). During diagnostic laparoscopy, the pelvic and abdominal cavity should be systematically investigated for the presence of endometriosis. This examination should include

a complete inspection and palpation, in a clockwise or counterclockwise fashion with a blunt probe, of the bowel, bladder, uterus, tubes, ovaries, cul-de-sac, and broad ligament (Fig. 29.1.). The type, location, and extent of all lesions and adhesions should be documented in the operative notes; ideally, the findings should be recorded on video or DVD (159). There is insufficient evidence to justify performing the laparoscopy at a specific time in the menstrual cycle, but to avoid underdiagnosis, it should not be performed during or within 3 months of hormonal treatment (159).

Characteristic findings include typical ("powder-burn" or "gunshot") lesions on the serosal surfaces of the peritoneum. These lesions are black, dark brown, or bluish nodules or small cysts containing old hemorrhage surrounded by a variable degree of fibrosis (Fig. 29.2.). Endometriosis can appear as subtle lesions (Fig. 29.3.), including red implants (petechial, vesicular, polypoid, hemorrhagic, red flamelike), serous or clear vesicles, white plaques or scarring, yellow-brown discoloration of the peritoneum, and subovarian adhesions (93,94,95,184,185). Histologic confirmation of the laparoscopic impression is essential for the diagnosis of endometriosis (186), not only for subtle lesions but also for typical lesions reported to be histologically negative in 24% of cases (187). **In the presenc**

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of ovarian endometrioma (greater than 3 cm in diameter) and deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy (159).

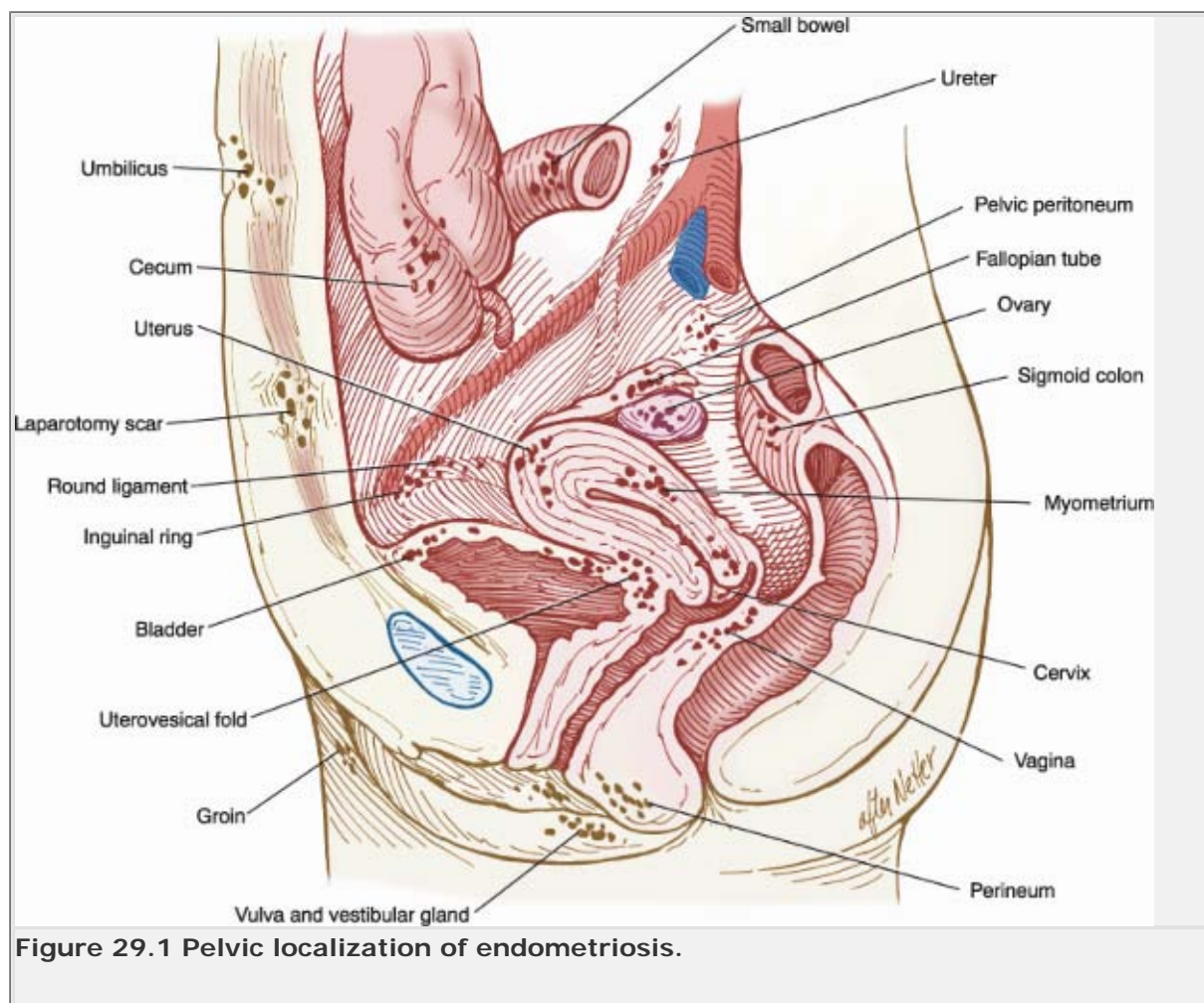


Figure 29.1 Pelvic localization of endometriosis.

Mild forms of deep endometriosis may only be detected by palpation under an endometriotic lesion or by discovery of a palpable mass beneath visually normal peritoneum, most notably in the posterior cul-de-sac (152) (Fig. 29.4.). At laparoscopy, deeply infiltrating endometriosis

may have the appearance of minimal disease, resulting in an underestimation of disease severity (188). Reduced Douglas depth and volume in women with deep endometriosis suggests that such lesions develop not in the rectovaginal septum but intraperitoneally and that burial of anterior rectal wall adhesions creates a false bottom, giving an erroneous impression of extraperitoneal origin (189). **The diagnosis of ovarian endometriosis is facilitated by careful inspection of all sides of both ovaries, which may be difficult when adhesions are present in more advanced stages of disease** (Fig. 29.5.). With superficial ovarian endometriosis, lesions can be both typical and subtle. Larger ovarian endometriotic cysts (endometrioma) are usually located on the anterior surface of the ovary and are associated with retraction, pigmentation, and adhesions to the posterior peritoneum. These ovarian endometriotic cysts often contain a thick, viscous dark brown fluid ("chocolate fluid") composed of hemosiderin derived from previous intraovarian hemorrhage. Because this fluid may also be found in other conditions, such as in hemorrhagic corpus luteum cysts or neoplastic cysts, biopsy and preferably removal of the ovarian cyst for histologic

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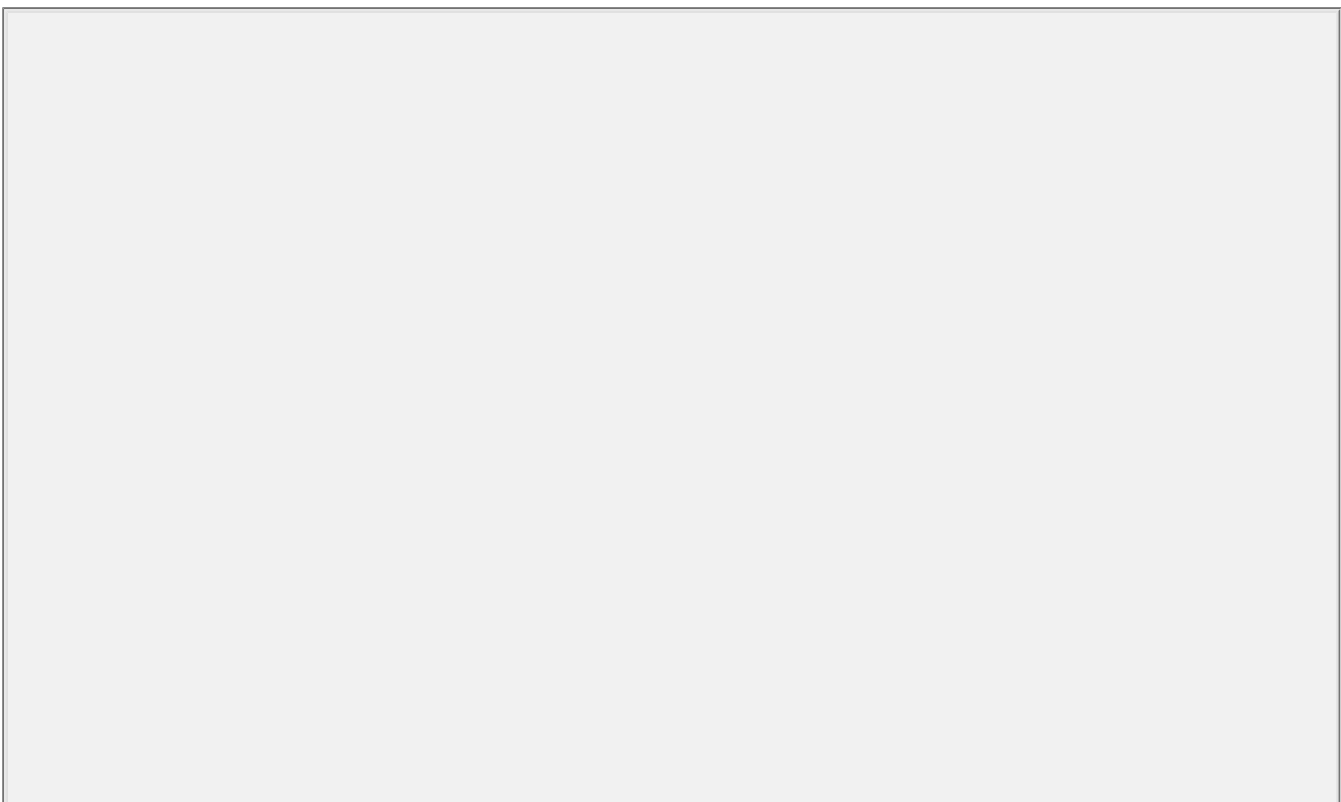
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confirmation are necessary for the diagnosis in the revised endometriosis classification of the American Society for Reproductive Medicine. If that is not possible, **the presence of an ovarian endometriotic cyst should be confirmed by the following features: cyst diameter of less than 12 cm, adhesion to pelvic sidewall or broad ligament, endometriosis on surface of ovary, and tarry, thick, chocolate-colored fluid content** (190). Ovarian endometriosis appears to be a marker for more extensive

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pelvic and intestinal disease. Exclusive ovarian disease is found in only 1% of endometriosis patients, with the remaining patients having mostly extensive pelvic or intestinal endometriosis (191).





A



B

Figure 29.2 Typical and subtle endometriotic lesions on peritoneum (photographs kindly donated by Dr Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium.) **A:** Typical black-puckered lesions with hypervascularization and orange polypoid vesicles. **B:** Red polypoid lesions with hypervascularization.



Figure 29.3 Ovarian endometriosis (photographs kindly donated by Dr Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium). **A:** Superficial ovarian endometriosis. **B:** Superficial ovarian endometriosis and endometrioma laparoscopic image prior to adhesiolysis. **C:** Laparoscopic image of uterus and right ovary with dark endometrioma. **D:** Ovarian endometriotic cystectomy **E:** Ovarian endometriotic cystectomy.

Histologic Confirmation

Histologic confirmation is essential in the diagnosis of endometriosis. In a study of 44 patients with chronic pelvic pain, endometriosis was laparoscopically diagnosed in 36%, but histologic confirmation was obtained in only 18%. This approach resulted in a low diagnostic accuracy of laparoscopic inspection with a positive predictive value of only 45%, explained by a specificity of only 77% (192).

Microscopically, endometriotic implants consist of endometrial glands and stroma, with or without hemosiderin-laden macrophages (Fig. 29.6.). It has been suggested, however, that using these stringent and unvalidated histologic criteria may result in significant underdiagnosis of endometriosis (2). Furthermore, problems in obtaining biopsies (especially small vesicles) and variability in tissue processing (step or partial instead of serial sectioning) may contribute to false-negative results. Endometrioid stroma may be more characteristic of endometriosis than endometrioid glands (193). The presence of stromal endometriosis, which contains endometrial stroma with hemosiderin-laden macrophages or hemorrhage, has been reported in women (186,187) and in baboons (101) and may represent a very early event in the pathogenesis of endometriosis. Isolated endometrial stromal cell nodules, immunohistochemically positive for vimentin and estrogen receptor, can be found in the absence of endometrial glands along blood or lymphatic vessels (194).

Different types of lesions may have different degrees of proliferative or secretory glandular activity (193). Vascularization, mitotic activity, and the three-dimensional structure of endometriosis lesions are key factors (195,196,197). Deep endometriosis has been described as a specific type of pelvic endometriosis characterized by proliferative strands of glands and stroma in dense fibrous and smooth muscle tissue (115). However, smooth muscles are

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also frequent components of endometriotic lesions on the peritoneum, ovary, rectovaginal septum, and uterosacral ligaments (198).

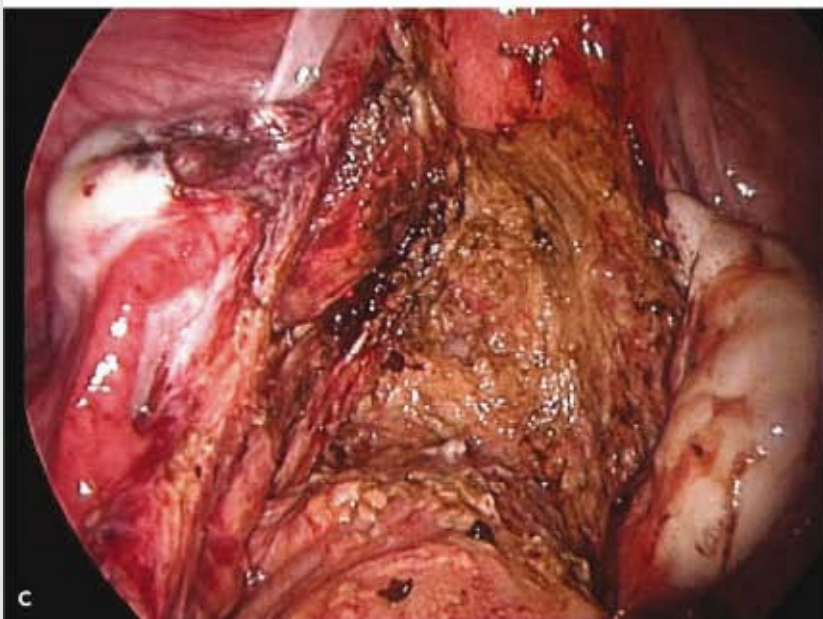
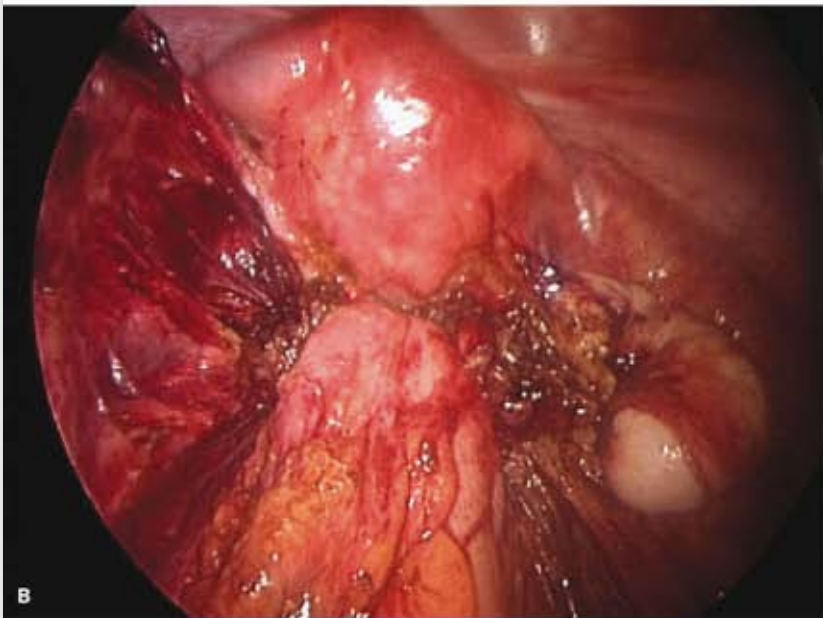
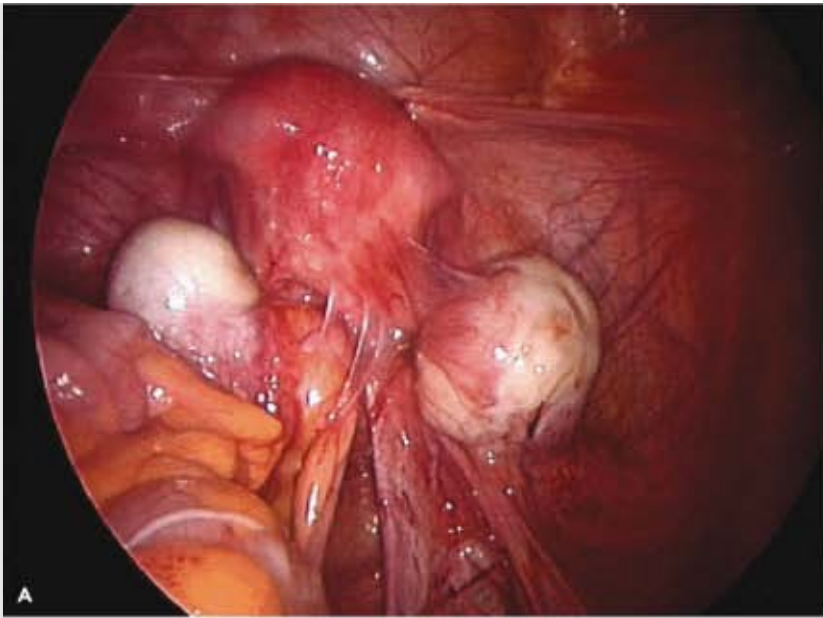


Figure 29.4 Laparoscopic excision of deep endometriosis from the cul-de-sac

(photographs kindly donated by Dr Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium). **A:** Extensive endometriosis with deep nodule at the right uterosacral ligament, masked by adhesions. **B:** Deep nodule still present in dense adhesion between rectum and uterosacral ligaments. **C:** Cul-de-sac after resection of deep nodule with CO² laser.

Microscopic endometriosis is defined as the presence of endometrial glands and stroma in macroscopically normal pelvic peritoneum. It is believed to be important in the histogenesis of endometriosis and its recurrence after treatment (199,200). The clinical relevance of microscopic endometriosis is controversial because it has not been observed uniformly. Using undefined criteria for what constitutes normal peritoneum, peritoneal biopsy specimens of 1 to 3 cm were obtained during laparotomy from 20 patients with moderate to severe endometriosis (200). Examination of the biopsy results with low-power scanning electron microscopy revealed unsuspected microscopic endometriosis in 25% of cases not confirmed by light microscopy. Peritoneal endometriotic foci have been demonstrated by light microscopy in areas that show no obvious evidence of disease (201). **In serial sections of laparoscopic biopsies of normal peritoneum, 10% to 15% of women were shown to have microscopic endometriosis, and endometriosis was found in 6% of those without macroscopic disease** (185,202,203).

In contrast, other studies have been unable to detect microscopic endometriosis in 2-mm biopsy specimens of visually normal peritoneum (92,204,205,206). Examination of larger samples (5–15 mm) of visually normal peritoneum has revealed microscopic endometriosis in only 1 of 55 patients studied (207). Similarly, a histologic study of serial sections through the entire pelvic peritoneum of visually normal peritoneum from baboons with and without disease indicated that microscopic endometriosis is a rare occurrence (208). **Therefore, it appears that macroscopically appearing normal peritoneum rarely contains microscopic endometriosis** (207).

Classification

The current classification system of endometriosis by the American Society of Reproductive Medicine is the former American Fertility Society (AFS) system (see

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Fig. 29.5.), which has been revised without major changes (131). It is based on the appearance, size, and depth of peritoneal and ovarian implants; the presence, extent, and type of adnexal adhesions; and the degree of cul-de-sac obliteration. **In the new classification system, the morphology of peritoneal and ovarian implants should be categorized as red (red, red-pink, and clear lesions), white (white, yellow-brown, and peritoneal defects), and black (black and blue lesions)..**

Patient's Name _____ Date _____
 Stage I (Minimal) - 1-5
 Stage II (Mild) - 6-15
 Stage III (Moderate) - 16-40
 Stage IV (Severe) - >40
 Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
 Recommended Treatment _____
 Prognosis _____

PERITONEUM	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
	Superficial	1	2	4
Deep	2	4	6	
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
POSTERIOR CUL-DE-SAC OBLITERATION		Partial	Complete	
		4	40	
OVARY	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____

Associated Pathology: _____

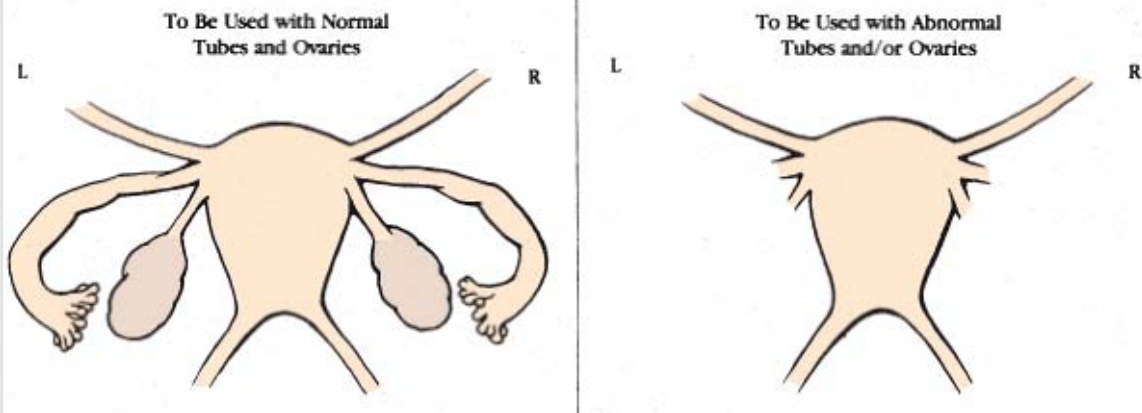


Figure 29.5 Revised American Society for Reproductive Medicine Classification. (From the American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis. *Am Soc Reprod Med* 1997;5:817-821.).

This system reflects the extent of endometriotic disease but has considerable intraobserver and interobserver variability (209,210). Because the revised classification of endometriosis is the only internationally accepted system, it appears to be the best available tool to describe objectively the extent of endometriosis and relate it to spontaneous evolution and to therapeutic outcomes (pain relief, enhancement of fertility).

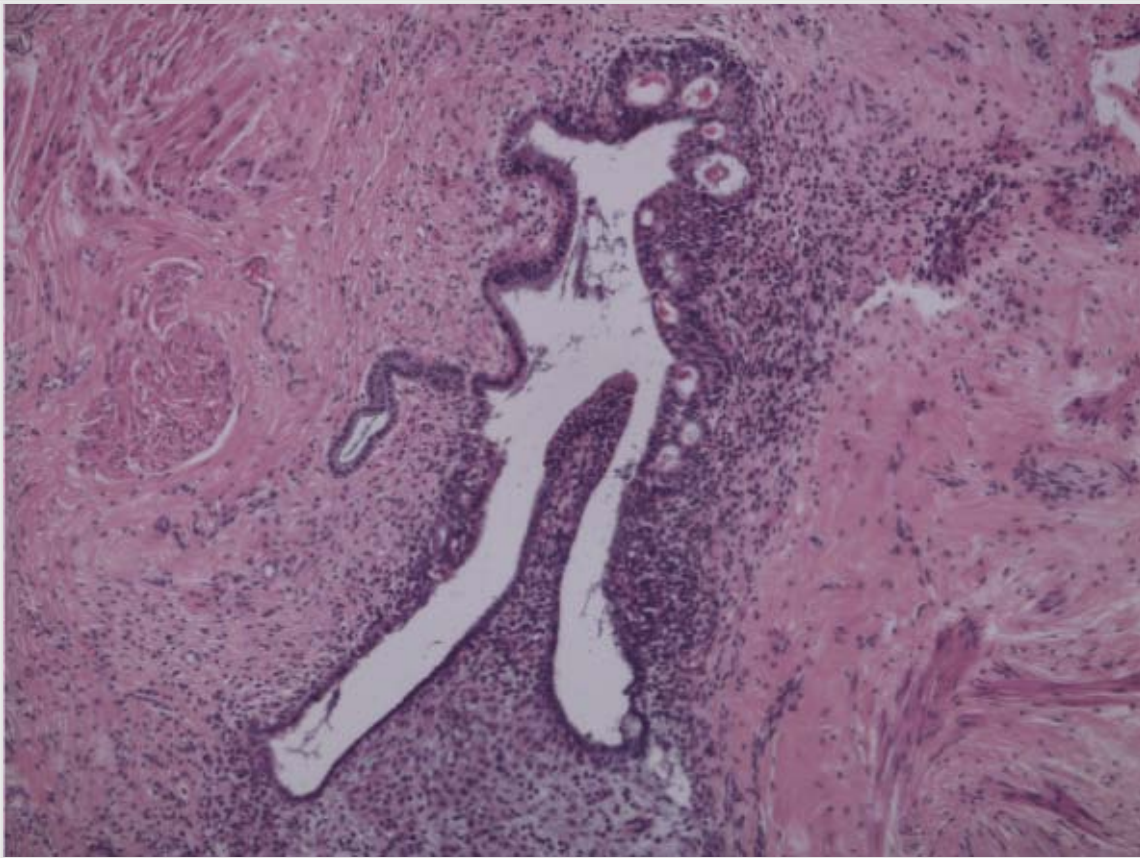


Figure 29.6 Histologic appearance of endometriosis: endometrial glandular epithelium, surrounded by stroma in typical lesion and clear vesicle..

The classification system has also been criticized because several investigators failed to find a correlation between it and endometriosis-related pain or infertility. This topic will be reviewed in "Results of Surgical Treatment."

Spontaneous Evolution

Endometriosis appears to be a progressive disease in a significant proportion (30%–60%) of patients. During serial observations, deterioration (47%), improvement (30%), or elimination (23%) was documented over a 6-month period (211). In another study, endometriosis progressed in 64%, improved in 27%, and remained unchanged in 9% of patients over 12 months (212). A third study of 24 women reported 29% with disease progression, 29% with disease regression, and 42% with no change over 12 months. Follow-up studies in both baboons and women (213,214,215) with spontaneous endometriosis over 24 months have demonstrated disease progression in all baboons and in 6 of 7 women. Several studies have reported that subtle lesions and typical implants may represent younger and older types of endometriosis, respectively. In a cross-sectional study, the incidence of subtle lesions decreased with age (216). This finding was confirmed by a 3-year prospective study that reported that the incidence, overall pelvic area involved, and volume of subtle lesions decreased with age, but in typical lesions, these parameters and the depth of infiltration increased with age (105). Remodeling of endometriotic lesions (transition between typical and subtle subtypes) has been reported to occur in women and in baboons, indicating that endometriosis is a dynamic condition (217,218). Several studies in women, cynomolgus monkeys, and rodents have shown that endometriosis is ameliorated after pregnancy (218,219,220,221).

The characteristics of endometriosis are variable during pregnancy, and lesions tend to enlarge during the first trimester but regress thereafter (222). Studies in baboons have revealed no change in the number or surface area of endometriosis lesions during the first two trimesters of pregnancy (223). These results do not exclude a beneficial effect that potentially may occur during the third trimester or in the immediate postpartum period. Establishment of a "pseudopregnant state" with exogenously administered estrogen and progestins was based on the belief that symptomatic improvement may result from decidualization of endometrial implants during pregnancy (224). This hypothesis, however, has not been substantiated.

Treatment

Treatment must be individualized, taking into consideration the clinical problem in its entirety, including the impact of the disease and the effect of its treatment on quality of life (159). Pain may persist despite seemingly adequate medical or surgical treatment of the disease. In such circumstances, a multidisciplinary approach involving a pain clinic and counseling should be considered early in the treatment plan (159). It also is important to involve the woman in all decisions, to be flexible in considering diagnostic and therapeutic approaches, and to maintain a good relationship with the patient. It may be appropriate to seek advice from more experienced colleagues or to refer the woman to a center with the necessary expertise to offer all available treatments in a multidisciplinary context, including advanced laparoscopic surgery and laparotomy (159). Because the management of severe or deeply infiltrating endometriosis is complex, referral is strongly recommended if disease of such severity is suspected or diagnosed (159).

Prevention

No strategies to prevent endometriosis have been uniformly successful. Although a reduced incidence of endometriosis has been reported in women who engaged in aerobic activity from an early age (16), the possible protective effect of exercise has not been investigated thoroughly. There also is insufficient evidence that oral contraceptive use offers protection against the development of endometriosis. In contrast, a recent report (225) showed an increased risk for endometriosis development in a select population of women taking oral contraceptives.

Regardless of the clinical profile (subfertility, pain, asymptomatic findings), treatment of endometriosis may be justified because endometriosis appears to progress in 30% to 60% of patients within a year of diagnosis and because it is not possible to predict in which patients it will progress (212). **Unfortunately, elimination of the endometriotic implants by surgical or medical treatment often provides only temporary relief. Therefore, in addition to eliminating the endometriotic lesions, the goal should be, more importantly, to treat the sequelae (pain and subfertility) often associated with this disease.**

Surgical Treatment

In most women with endometriosis, preservation of reproductive function is desirable. Therefore, the least invasive and least expensive approach that is effective should be used. Depending on the severity of disease, diagnosis and removal of endometriosis should be performed simultaneously at the time of surgery provided preoperative consent has been obtained (159,226,227,228,229). **The goal of surgery is to excise all visible**

endometriotic lesions and associated adhesions—peritoneal lesions, ovarian cysts, deep rectovaginal endometriosis—and to restore normal anatomy. In most women, laparoscopy can be used, and this technique decreases cost, morbidity, and the possibility of recurrence of adhesions postoperatively. **Laparotomy should be reserved for patients with advanced—state**

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disease who cannot undergo a laparoscopic procedure and for those in whom fertility conservation is not necessary.

Peritoneal Endometriosis

Endometriosis lesions can be removed during laparoscopy by surgical excision with scissors, bipolar coagulation, or laser methods (CO₂ laser, potassium–titanium–phosphate laser, or argon laser). Although some surgeons claim that the CO₂ laser is superior because it causes only minimal thermal damage, no evidence is available to show the superiority of one technique over another. Comparable cumulative pregnancy rates have been reported after treatment of mild endometriosis with laparoscopic excision and electrocoagulation (230).

Ovarian Endometriosis

Superficial ovarian lesions can be vaporized. Small ovarian endometrioma (<3 cm in diameter) can be aspirated, irrigated, and inspected with ovarian cystoscopy for intracystic lesions; their interior wall can be vaporized to destroy the mucosal lining of the cyst (231). Large (>3 cm in diameter) ovarian endometrioma should be aspirated, followed by incision and removal of the cyst wall from the ovarian cortex. To prevent recurrence, the cyst wall of the endometrioma must be removed, and normal ovarian tissue must be preserved..

Although as little as one tenth of an ovary is enough to preserve function and fertility (232), there is increasing concern that ovarian cystectomy with concomitant removal or destruction of primordial follicles may reduce ovarian volume and reserve and diminish fertility. A recent study reported reduced follicular response in natural and clomiphene citrate–stimulated cycles, but not in gonadotropin–stimulated cycles, in women younger than 35 years of age who underwent cystectomy compared with controls of similar age with normal ovaries (233). Therefore, it has been proposed to replace cystectomy by fenestration and coagulation of the inner wall of the endometriotic ovarian cyst. In one study, cumulative clinical pregnancy rates and recurrence rates were comparable in women treated with cystectomy and with fenestration and coagulation after 36 months, but conception occurred more quickly in the fenestration and coagulation group (234). A more recent case–control study in 231 patients reported a lower cumulative reoperation rate in the cyst excision group than in the fenestration and coagulation group after 18 (6% versus 22%) and 42 (24% versus 59%) months of follow-up (235). A randomized controlled trial demonstrated that pain and subfertility caused by ovarian endometrioma were improved more by cystectomy than by fenestration and coagulation (236). A reduced recurrence of pain after 2 years (odds ratio [OR], 0.2; confidence interval [CI], 0.05–0.77), an increased pain–free interval after operation (19 months versus 9.5 months), and an increased pregnancy rate (67% versus 23%) were found in the cystectomy group when compared with the fenestration and coagulation group (236). In another recent study (237), coagulation or laser vaporization of endometriomas without excision of the pseudocapsule was associated with a significantly increased risk of cyst recurrence. Laparoscopic cystectomy for ovarian endometriomas greater than 4 cm diameter improves fertility compared with drainage and coagulation (238,239).

Therefore, based on the current evidence, **ovarian cystectomy appears to be the method**

of choice..

Adhesiolysis

The removal of endometriosis-related adhesions (adhesiolysis) should be performed carefully. Routine use of pharmacologic or liquid agents to prevent postoperative adhesions after fertility surgery cannot be recommended based on evidence from randomized controlled trials (240).

Preoperative Hormonal Treatment

In patients with severe endometriosis, it has been recommended that surgical treatment be preceded by a 3-month course of medical treatment to reduce vascularization and nodular size (152). However, **a recent randomized study comparing 3 months of preoperative treatment with GnRH and no treatment in 75 women with moderate to severe endometriosis failed to show a significant difference in ease of surgery between the two groups** (241).

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Deep Rectovaginal and Rectosigmoidal Endometriosis

The surgical excision of deep rectovaginal and rectosigmoidal endometriosis is difficult and can be associated with major complications. Postoperative bowel perforations with peritonitis have been reported in 2% to 3% of cases (242).

Preoperative investigations, including gynecologic ultrasonography, intravenous pyelography (to exclude ureteral endometriosis), and colon contrast radiography (to exclude transmural rectosigmoidal endometriosis), are essential, and MRI may be useful in specific cases. Preoperative laxatives, starch-free diet, and full bowel preparation are needed to allow perioperative bowel suturing, if needed. To allow complete excision of rectovaginal endometriosis, 6% of patients needed bowel wall resection, and 14% required partial resection of the posterior vaginal fornix (242). Segmental rectosigmoid resection can be performed by laparotomy, laparoscopy with intracorporeal suturing, or by laparoscopically assisted vaginal technique (243). The latter technique appears to be faster than laparoscopy with intracorporeal suturing and cheaper than laparotomy because of decreased hospital stay and lower operating room charges (243), but more studies are needed to confirm this impression. Ureter stents may be required before excision of peritoneal endometriosis surrounding the ureter. A multidisciplinary approach involving gynecologic and gastroenterologic surgeons and urologists is desirable. More long-term follow-up after surgery for colorectal endometriosis is needed to document complications, recurrences, and long-term effects on pain and fertility.

Oophorectomy and Hysterectomy

Radical procedures such as oophorectomy or total hysterectomy are indicated only in severe situations and can be performed either laparoscopically or, more commonly, by laparotomy. However, it is important to note that women aged 30 years or younger at the time of hysterectomy for endometriosis-associated pain are more likely than older women to have residual symptoms, to report a sense of loss, and to report more disruption from pain in different aspects of their lives (244). If a hysterectomy is performed, bilateral salpingo-oophorectomy should be considered as well (245), and all visible endometriotic tissue should be removed at the same time (246).

Postoperative Hormone Therapy

Postoperative hormone therapy with estrogen is required after bilateral oophorectomy, and there is a negligible risk for renewed growth of residual endometriosis (247). To reduce this risk, hormone therapy should be withheld until 3 months after surgery. The addition of progestins to this regimen protects the endometrium. However, the decision to start hormone therapy with a combination of estrogen and progestin should be balanced against the increased risk of breast cancer and heart disease associated with hormone therapy.

Some cases of adenocarcinoma have been reported, presumably arising from endometriosis lesions remaining in women treated with unopposed estrogen (232).

Results of Surgical Treatment

Pain

The outcome of surgical therapy in patients with endometriosis and pain is influenced by many psychological factors relating to personality, depression, and marital and sexual problems. **There is a significant placebo response to surgical therapy: diagnostic laparoscopy without complete removal of endometriosis may alleviate pain in 50% of patients** (248,249,250). Similar results have been reported using oral placebos (251). Although some reports have claimed pain relief with laser laparoscopy in 60% to 80% of patients with very low morbidity, none was prospective or controlled and, thus, did not allow a definitive conclusion regarding treatment efficacy (152,252,253,254,255).

Endometriosis Stage and Pain Relief after Surgery

In patients with pain, the endometriosis stage was not related to pain symptoms in several studies (256,257).

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However, more recent studies reported a positive correlation between endometriosis stage and endometriosis-related dysmenorrhea or chronic pelvic pain (258,259).

In a prospective, controlled, randomized, double-blind study, surgical therapy (ablation of endometriotic lesions and laparoscopic uterine nerve ablation [LUNA]) was shown to be superior to expectant management 6 months after treatment of mild and moderate endometriosis (248). In women with mild and moderate disease treated with laser, 74% achieved pain relief. Treatment was least effective in women with minimal disease. There were no reported operative or laser complications (248). There is no evidence that LUNA is a necessary part of this treatment (260) because LUNA by itself has no effect on dysmenorrhea associated with endometriosis (237). One year later, symptom relief was still present in 90% of those who responded initially (213,248). Patients with severe disease were not included (248) because it had previously been shown that surgery resulted in pain relief in 80% of patients who did not respond to medical therapy (261).

These results suggest that laser laparoscopy may be effective for the treatment of pain associated with mild to severe endometriosis. In women with minimal endometriosis, laser treatment may limit progression of disease.

Effect of Preoperative and Postoperative Treatment

Hormonal therapy before surgery improves endometriosis scores, but there is insufficient evidence that it has any effect on pain relief after the operation (262).

Some evidence from randomized controlled trials supports the postoperative medical treatment of pain associated with endometriosis for 6–12 months. Postoperative GnRH treatment resulted in reduced pain scores and in a delay of pain recurrence for more than 12 months if the agonists were given for 6 months but not if they were only administered for 3 months (263,264,265). Similarly, postoperative hormonal treatment with *danazol*, 100 mg/day (low dose), for 12 months after surgery for moderate to severe endometriosis resulted in a significantly lower pain score in the treated group when compared with the placebo group. In contrast, postoperative high-dose *danazol*, 600 mg/day for 3 months, was not superior to expectant management with respect to pain recurrence in an identical patient population (266). According to a recent Cochrane review (262), compared with surgery alone or surgery plus placebo, postoperative hormonal treatment does not reduce pain recurrence at 12 or 24 months and has no effect on disease recurrence 263–266, 268, 270, 271, 273.

Subfertility

Advanced Endometriosis and Pregnancy Outcome after Surgery

When endometriosis causes mechanical distortion of the pelvis, surgery should be performed to achieve reconstruction of normal pelvic anatomy. **Laparoscopic cystectomy for ovarian endometriomas greater than 4 cm diameter improves fertility compared with drainage and coagulation** (238,239).

The success of surgery in relieving infertility is probably related to the severity of endometriosis. A recent retrospective multicenter analysis (271) reported cumulative pregnancy rates of 39%, 31%, 30%, and 25% in patients with endometriosis stages I, II, III, and IV, respectively, 12 months after surgical treatment. Although there appeared to be a negative correlation between stage of endometriosis and fertility outcome, no significant difference was found between the four groups in this study. However, the study had many limitations, including retrospective design, lack of well-defined definition of male factor infertility as potential bias, multicenter data with significant interobserver variability, inclusion of only a limited number of patients with substantial adhesive disease, variable infertility treatment after 6 months of follow-up, and absence of a control group.

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A somewhat higher cumulative intrauterine pregnancy rate has been reported in 30 women with deep uterosacral endometriosis after surgery: 48% after 12 months (47% for AFS stages I to II and 46% for AFS stages III to IV) (276). A cumulative pregnancy rate of 24% was reported in patients 9 months after undergoing reoperation for stage III to IV endometriosis (277).

Other investigators reported a negative correlation between stage of endometriosis and fertility after surgical treatment. In an older study, using an older classification system, a significant decrease in fecundability was seen in women with severe or extensive endometriosis compared with women with mild or moderate disease (278,279). In a more recent study (280), the negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis was statistically significant. Other studies have reported a significant negative correlation between endometriosis stage and pregnancy rate and decreased pregnancy rates when the

revised scores exceeded 70 (281,282).

Preoperative and Postoperative Medical Treatment

Preoperative medical treatment with *danazol*, GnRH agonists, or progestins may be useful to reduce the extent of endometriosis in patients with advanced disease. **Postoperative medical treatment is rarely indicated because it does not work based on randomized trials, because it prevents pregnancy, and because the highest pregnancy rates occur during the first 6 to 12 months after conservative surgery** (264,265). If pregnancy does not occur within 2 years of surgery, there is little chance of subsequent fertility (283).

Minimal to Mild Endometriosis and Fertility after Surgery

Surgical management of infertile women with minimal to mild endometriosis is controversial. The cumulative pregnancy rate after 5 years without therapy has been reported to be as high as 90% in women with minimal or mild endometriosis (284). This is comparable to the 93% rate reported in women who do not have endometriosis. Laparoscopic destruction of endometriosis has been reported to improve fertility in patients with minimal to mild disease (285,286,287), but not all investigators share this conclusion (288,289,290). It has been hypothesized that the MFR is higher during the first 6 to 12 months after laparoscopic surgery than with expectant management (291,292).

Two randomized controlled studies have evaluated the effect of surgical treatment of endometriosis on fertility parameters (144,145). **One study** (144) **reported that laparoscopic surgery enhanced fecundity in infertile women with minimal or mild endometriosis.** They studied 341 infertile women, 20 to 39 years of age, with minimal or mild endometriosis. During diagnostic laparoscopy, the women were randomly assigned to undergo resection or ablation of visible endometriosis or diagnostic laparoscopy only. They were followed for 36 weeks after the laparoscopy or, for those who became pregnant during that interval, for up to 20 weeks of pregnancy. The study objects were recruited among infertile women scheduled for diagnostic laparoscopy with strict eligibility criteria. The women in the study had no previous surgical treatment for endometriosis and no medical treatment for endometriosis in the previous 9 months and no other medical or surgical treatment for infertility in the previous 3 months. They had no history of pelvic inflammatory disease and no severe pelvic pain precluding expectant management. The diagnosis of endometriosis required the presence of one or more typical bluish or black lesions. The stage of endometriosis was determined according to the revised American Society of Reproductive Medicine classification. **During diagnostic laparoscopy, the women were randomly assigned to undergo resection or ablation of visible endometriosis or diagnostic laparoscopy only. They found that resection or ablation of minimal and mild endometriosis increased the likelihood of pregnancy in infertile women.** In the treated group, 31% of the patients became pregnant, compared with 18% in the nontreated group ($p=0.006$).

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In a multicenter study in Italy, a similar study design was used to compare the effect of diagnostic laparoscopy with surgical resection and ablation of visible endometriosis (on fertility parameters) in infertile women with minimal to mild endometriosis (145). Eligible patients were women aged less than 36 years who were trying to conceive and had a laparoscopically confirmed diagnosis of minimal or mild endometriosis. None of the women had had therapy for endometriosis or infertility. Treatment was randomly allocated during laparoscopy. There was a follow-up period of 1 year after the laparoscopy. **The results of this study did not show a beneficial effect of surgery regarding fertility.** During the

follow-up period after laparoscopy, no statistically significant differences in conception and live-birth rates were observed in the treated group (24% and 20%, respectively) and in the control group (29% and 22%, respectively).

Prognosis with Surgical Treatment

Based on the aforementioned studies, and taking into account the larger patient population in the Canadian multicenter study, **surgical treatment of minimal to mild endometriosis appears to offer a small but significant benefit with regard to fertility outcome** (130,159,289). Furthermore, the surgical removal of peritoneal endometriosis may also be important to prevent progression of endometriosis. However, care is needed to prevent adhesion formation that could result as a consequence of overenthusiastic excision of minimal to mild endometriosis.

Medical Treatment

Empirical Treatment

If the patient desires treatment of pain symptoms suggestive of endometriosis in the absence of a definitive diagnosis, a therapeutic trial of a hormonal medication to reduce menstrual flow is appropriate. Empirical treatment for pain presumed to be due to endometriosis in the absence of a definitive diagnosis includes counseling, analgesia, nutritional therapy, progestins, or combined oral contraceptives.

It is unclear whether combined oral contraceptives should be taken in a conventional, continuous, or tricycle regimen. A GnRH agonist may be taken, but this class of drug is more expensive and associated with more side effects and concerns about bone density than oral contraceptives (159).

Dysmenorrhea

Generally, women suffering from dysmenorrhea are treated with analgesics; many women treat themselves with over-the-counter oral analgesics. **In a recent systematic Cochrane review evaluating the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for primary dysmenorrhea** (290), primary dysmenorrhea was described as menstrual pain without organic pathology (see Chapter 15). Exclusion of pelvic pathology was based on physical examination alone. It can be argued that some of these women with so-called primary dysmenorrhea probably in fact had endometriosis. **It was concluded that NSAIDs, except *niflumic acid*, were more effective than placebo for pain relief** (290), **but there was insufficient evidence to suggest whether any individual NSAID was more effective than another.** In another review, selective cyclo-oxygenase-2 inhibitors *rofecoxib* and *valdecoxib* were found to be as effective as *naproxen* and more effective than placebo for the treatment of primary dysmenorrhea (291). However, concerns have been raised about the safety of these medications, and its manufacturers have recently withdrawn *rofecoxib* from the market.

According to a systematic review (292) based on two relatively small randomized controlled trials comparing *paracetamol* and *co-proxamol* with placebo, respectively, *co-proxamol* (*paracetamol* 650 mg and *dextropropoxyphen* 65 mg) but not *paracetamol*

(500 mg 4 times daily) was more effective than placebo in reducing pain. This observation can possibly be explained by the suboptimal dosage of *paracetamol* used.

Pain

Considering that endometriosis is a chronic inflammatory disease, anti-inflammatory drugs would appear to be effective for treatment (see Chapter 15). **Nonsteroidal anti-inflammatory drugs may be effective in reducing endometriosis associated pain** (159,293,294,295). Although NSAIDs have been used extensively and have often been the first line therapy for reduction of endometriosis-related pain, the analgesic effect of NSAIDs has not been studied extensively. Only one small, double-blind, placebo-controlled, four-period, crossover clinical study has been published (294). This study showed complete or substantial pain relief of endometriosis-related dysmenorrhea in 83% of cases treated with *naproxen* compared with 41% in cases treated with placebo. Women who received *naproxen* needed significantly fewer supplemental analgesics compared to women taking placebo.

Endometriosis-related pain is nociceptive (296), but persistent nociceptive input from endometriotic lesions leads to central sensitization manifested by somatic hyperalgesia and increased referred pain. The effectiveness of NSAIDs in the reduction of endometriosis-related pain may be explained by both a local antinociceptive effect and a reduced central sensitization in addition to the anti-inflammatory effect. However, NSAIDs have significant side effects, including gastric ulceration and possible inhibition of ovulation. Prostaglandins also are involved in the follicle rupture mechanism at ovulation, which is why women who wish to become pregnant should not take NSAIDs at the time of ovulation (297).

Nonhormonal Medical Therapy

Modulation of Cytokines

In rats with experimental endometriosis, recombinant human TNF- α -binding protein can reduce 64% of the size of endometriosis-like peritoneal lesions (298). Similarly, a recent prospective randomized placebo- and drug-controlled study in baboons showed that recombinant human TNF- α -binding protein effectively inhibits the development of endometriosis and endometriosis-related adhesions (57) and is effective in the treatment of spontaneous endometriosis in baboons (299).

In mice with experimental endometriosis, a placebo-controlled double-blind study showed that intraperitoneal or subcutaneous injection of recombinant interferon- α 2b resulted in smaller endometriotic lesions when compared with the placebo control group (300). In rats with experimental endometriosis, regression of endometrial explants was observed after treatment with immune-enhancing modulators *loxoribine* and *levamisole* (301).

Anti-inflammation

In the future, leukotriene receptor antagonists could be of use in patients with endometriosis who do not respond to prostaglandin synthetase inhibitors (302). In humans, a randomized placebo-controlled trial of oral *pentoxifylline*, 800 mg/day for 12 months, reported after life-table analysis a similar overall pregnancy rate in treated patients (31%) and in controls (18.5%) (303).

Inhibition of Matrix Metalloproteinase

In nude mice, suppression of MMPs by progesterone or by a natural inhibitor slows the establishment of ectopic lesions by human endometrium (304). Thus far, no clinical reports

have been published.

New Developments

Many substances potentially capable of modulating immunologic or inflammatory mechanisms involved in the onset or progression of the disease could be the targets for future research in endometriosis (305,306).

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Hormonal Medical Treatment

Because estrogen is known to stimulate the growth of endometriosis, hormonal therapy has been designed to suppress estrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding. Implants of endometriosis react to gonadal steroid hormones in a manner similar but not identical to normally stimulated ectopic endometrium. Ectopic endometrial tissue displays histologic and biochemical differences from normal ectopic endometrium in characteristics such as glandular activity (proliferation, secretion), enzyme activity (17 β -hydroxysteroid dehydrogenase), and steroid (estrogen, progestin, and androgen) hormone receptor levels.

There is strong evidence that suppression of ovarian function for 6 months reduces pain associated with endometriosis. Combined oral contraceptives *danazol*, *gestrinone*, *medroxyprogesterone acetate*, and GnRH agonists are all equally effective but their side-effect and cost profiles differ (159,306,307,308,309).

The use of *diethylstilbestrol*, *methyltestosterone*, or other androgens is no longer advocated because they lack efficacy, have significant side effects, and pose risks to the fetus if pregnancy occurs during therapy. A new generation of aromatase inhibitors, estrogen receptor modulators, and progesterone antagonists may offer new hormonal treatment options in the future. Recent progress in the understanding of the pathogenesis of endometriosis has led to the expectation that new pharmaceutical agents affecting inflammation, angiogenesis, and MMP activity may prevent or inhibit the development of endometriosis.

Oral Contraceptives

Continuous Administration

Manipulation of the endogenous hormonal milieu is the basis for the medical management of endometriosis. The treatment of endometriosis with continuous low-dose monophasic combination contraceptives (one pill per day for 6–12 months) was originally used to induce pseudopregnancy caused by the resultant amenorrhea and decidualization of endometrial tissue (224). Kistner was the first to introduce the concept of an adynamic endometrium through elimination of the normal cyclic hormonal changes characteristic of the menstrual cycle (310). **This induction of a pseudopregnancy state with combination oral contraceptive pills has been shown to be effective in reducing dysmenorrhea and pelvic pain.** In addition, the subsequent amenorrhea induced by oral contraceptives could potentially reduce the amount of retrograde menstruation (one of the risk factors proposed in the etiology of endometriosis), decreasing the risk for disease progression. Pathologically, oral contraceptive use is associated with decidualization of endometrial tissue, necrobiosis, and possibly absorption of the endometrial tissue (311). Unfortunately, there is no convincing evidence that medical therapy with oral

contraceptives offers definitive therapy. Instead, the endometrial implants survive the induced atrophy and, in most patients, reactivate after termination of treatment.

Any low-dose combination oral contraceptive containing 30 to 35 µg of ethinyl estradiol used continuously can be effective in the management of endometriosis.

The objective of the treatment is the induction of amenorrhea, which should be continued for 6 to 12 months. Symptomatic relief of dysmenorrhea and pelvic pain is reported in 60% to 95% of patients (312,313). After a first-year recurrence rate of 17% to 18%, a 5% to 10% annual recurrence rate has been observed. In addition, a posttreatment pregnancy rate of up to 50% can be expected. Although oral contraceptives are effective in inducing a decidualized endometrium, the estrogenic component in oral contraceptives may potentially stimulate endometrial growth and increase pelvic pain in the first few weeks of treatment. The long-term significance of this effect remains to be determined. **Oral contraceptives are less costly than other treatments and may be helpful in the short-term management of endometriosis with potential long-term benefits in some women.**

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Cyclic Administration

There is no convincing evidence that cyclic use of combination oral contraceptives provides prophylaxis against either the development or recurrence of endometriosis. Estrogens in oral contraceptives potentially may stimulate the proliferation of endometriosis. The reduced menstrual bleeding that often occurs in women taking oral contraceptives may be beneficial to women with prolonged, frequent menstrual bleeding, which is a known risk factor for endometriosis (16). Further research is warranted to assess the effect of low-dose oral contraceptives in preventing endometriosis and in treating associated pain. In a randomized controlled study, a cyclic 21-day oral contraceptive (*ethinyl estradiol* 20 µg plus *desogestrel* 0.15 mg) combined with very-low-dose *danazol* (50 mg/day) was less effective in relief of dysmenorrhea than depot *medroxyprogesterone* acetate (150 mg every 3 months) (314).

Progestins

Progestins may exert an antiendometriotic effect by causing initial decidualization of endometrial tissue followed by atrophy. They can be considered as the first choice for the treatment of endometriosis because they are as effective as *danazol* or GnRH analogues and have a lower cost and a lower incidence of side effects than these agents (315).

There is no evidence that any single agent or any particular dose is preferable to another. The effective doses of several progestins are summarized in Table 29.1. In most studies, the effect of treatment has been evaluated after 3 to 6 months of therapy. *MPA* has been the most studied agent. It is effective in relieving pain starting at a dose of 30 mg/day and increasing the dose based on the clinical response and bleeding patterns (316,317). However, a recent randomized placebo-controlled study reported a significant reduction

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in stages and scores of endometriosis in both the placebo group and the group treated with *MPA*, 50 mg/day, and placebo at laparoscopy within 3 months after cessation of therapy (318). These findings raise questions about the need for medical therapy.

Table 29.1 Medical Treatment of Endometriosis–Associated Pain: Effective Regimens (Usual Duration: 6 Months)

	<i>Administration</i>	<i>Dose</i>	<i>Frequency</i>
Progestogens			
<i>Medroxyprogesterone acetate</i>	PO	30 mg	Daily
<i>Megestrol acetate</i>	PO	40 mg	Daily
<i>Lynoestrenol</i>	PO	10 mg	Daily
<i>Dydrogesterone</i>	PO	20–30 mg	Daily
Antiprogestins			
<i>Gestrinone</i>	PO	1.25 or 2.5 mg	Twice weekly
<i>Danazol</i>	PO	400 mg	Daily
Gonadotropin–Releasing Hormone			
<i>Leuprolide</i>	SC	500 mg	Daily
	IM	3.75 mg	Monthly
<i>Goserelin</i>	SC	3.6 mg	Monthly
<i>Buserelin</i>	IN	300 µg	Daily
	SC	200 µg	Daily
<i>Nafarelin</i>	IN	200 µg	Daily
<i>Triptorelin</i>	IM	3.75 mg	Monthly

PO, oral; SC, subcutaneous; IM, intramuscular; IN, intranasal.

Medroxyprogesterone acetate (150 mg) given intramuscularly every 3 months is also effective for the treatment of pain associated with endometriosis, but it is not indicated in infertile women because it induces profound amenorrhea and anovulation, and a varying length of time is required for ovulation to resume after discontinuation of therapy. *Megestrol acetate* has been administered in a dose of 40 mg/day with good results (319). Other treatment strategies have included *dydrogesterone* (20 to 30 mg/day, either continuously or on days 5 to 25) and *lynestrenol* (10 mg/day). The effectiveness of natural progesterone has not been evaluated.

Side effects of progestins include nausea, weight gain, fluid retention, and breakthrough bleeding caused by hypoestrogenemia. Breakthrough bleeding, although common, is usually corrected by short-term (7-day) administration of estrogen. Depression and other mood disorders are a significant problem in about 1% of women taking these medications.

Intrauterine Progesterone Treatment

Local progesterone treatment of endometriosis–associated dysmenorrhea with a *levonorgestrel*-releasing intrauterine system for 12 months has resulted in a significant reduction in dysmenorrhea, pelvic pain, and dyspareunia; a high degree of patient satisfaction; and a significant reduction in the volume of rectovaginal endometriotic nodules (320,321). These promising results have been confirmed in other studies (322), even after 3 years of treatment (323). This type of local treatment may become a more important option if a long-term medical suppression of endometriosis is needed.

Progesterone Antagonists

Progesterone antagonists and progesterone receptor modulators may suppress endometriosis based on their antiproliferative effects on the endometrium, without the risk for hypoestrogenism

or bone loss that occurs with GnRH treatment. These products are soon to be introduced in the United States, but their clinical effectiveness remains to be proved.

Mifepristone

Mifepristone (RU-486) is a potent antiprogestagen with a direct inhibitory effect on human endometrial cells and, in high doses, an antiglucocorticoid action (324). The recommended dose for endometriosis is 25 to 100 mg/day. In uncontrolled studies, *mifepristone*, 50 to 100 mg/day, reduced pelvic pain and induced 55% regression of the lesions without significant side effects (325,326). In an uncontrolled pilot study, *mifepristone*, 5 mg/day, resulted in pain improvement, but there was no change in endometriosis lesions, suggesting that this dosage is probably too low (327).

Onapristone

Progesterone antagonists *onapristone* (ZK98299) and ZK136799, used in the treatment of rats with surgically induced endometriosis, resulted in a remission in 40% to 60% of treated animals. In animals with persistent endometriosis, growth inhibition was obtained in 48% and 85% of endometriotic lesions after therapy with *onapristone* and ZK136799, respectively (328).

Other Progesterone Antagonists

The chemical synthesis and pharmacologic characterization of a highly potent progesterone antagonist, ZK230211, have been reported, with little or no other endocrinologic effects. ZK230211 is active on both progesterone receptors A and B (329). In primates, this drug has been reported to block ovulation and menstruation at all effective doses (330), whereas another progesterone antagonist, ZK137316, allowed ovulation but blocked menstruation in a dose-dependent fashion. All progesterone antagonist-treated animals maintained normal follicular phase concentration

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of estradiol and returned to menstrual cyclicity within 15 to 41 days after treatment (330). Both progesterone antagonists block unopposed estrogen action on the endometriosis through their antiproliferative effect.

Gestrinone

Gestrinone is a 19-nortestosterone derivative with androgenic, antiprogestagenic, antiestrogenic, and antigonadotropic properties. It acts centrally and peripherally to increase free testosterone and reduce sex hormone-binding globulin levels (androgenic effect), reduce serum estradiol values to early follicular phase levels (antiestrogenic effect), reduce mean LH levels, and obliterate the LH and follicle-stimulating hormone (FSH) surge (antigonadotropic effect). *Gestrinone* causes cellular inactivation and degeneration of endometriotic implants but not their disappearance (331). Amenorrhea occurs in 50% to 100% of women and is dose dependent.

Resumption of menses generally occurs 33 days after discontinuing the medication (332,333). An advantage of gestrinone is its long half-life (28 hours) when given orally. The standard dose has been 2.5 mg twice a week. Although it has been reported that 1.25 mg twice weekly is equally effective (334), a more recent randomized study demonstrated in women with mild to moderate endometriosis that 2.5 mg *gestrinone*, twice weekly for 24 weeks, is more effective and has a better effect on bone mass (+7% versus -7%) when compared with 1.25 mg *gestrinone*, 2 times weekly for 24 weeks (335).

The clinical side effects of gestrinone are dose dependent and similar to but less intense than those caused by *danazol* (332). They include nausea, muscle cramps, and androgenic effects such as weight gain, acne, seborrhea, and oily hair and skin.

In a multicenter, randomized, double-blind study, *gestrinone* was as effective as GnRH for the treatment of pelvic pain associated with endometriosis (336). However, *gestrinone* has fewer side effects and has the added advantage of twice-weekly administration. Pregnancy is contraindicated while taking gestrinone because of the risk for masculinization of the fetus.

Danazol

Danazol is not more effective than other available medications to treat

endometriosis. Recognized pharmacologic properties of *danazol* include suppression of GnRH or gonadotropin secretion, direct inhibition of steroidogenesis, increased metabolic clearance of estradiol and progesterone, direct antagonistic and agonistic interaction with endometrial androgen and progesterone receptors, and immunologic attenuation of potentially adverse reproductive effects (337,338). The multiple effects of *danazol* produce a high-androgen, low-estrogen environment (estrogen levels in the early follicular to postmenopausal range) that does not support the growth of endometriosis, and the amenorrhea that is produced prevents new seeding of implants from the uterus into the peritoneal cavity.

The immunologic effects of danazol have been studied in women with endometriosis and adenomyosis and include a decrease in serum immunoglobulins, a decrease in serum C3, a rise in serum C4 levels, decreased serum levels of autoantibodies against various phospholipid antigens, and decreased serum levels of CA125 during treatment (165,166,178,179,180,181,339,340). *Danazol* inhibits peripheral blood lymphocyte proliferation in cultures activated by T-cell mitogens but does not affect macrophage-dependent T-lymphocyte activation of B lymphocytes (338). *Danazol* inhibits interleukin-1 and TNF production by monocytes in a dose-dependent manner, and suppresses macrophage- and monocyte-mediated cytotoxicity of susceptible target cells in women with mild endometriosis (341,342). These immunologic findings may be important in the remission of endometriosis with danazol treatment and may offer an explanation of the effect of *danazol* in the treatment of a number of autoimmune diseases, including hereditary

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angioedema (343), autoimmune hemolytic anemia (344), systemic lupus erythematosus (345), and idiopathic thrombocytopenic purpura (346,347). Doses of 800 mg/day are frequently used in North America, whereas 600 mg/day is commonly prescribed in Europe and Australia. It appears that the absence of menstruation is a better indicator of response than drug dose. A practical strategy for the use of *danazol* is to start treatment with 400 mg daily (200 mg twice a day) and increase the dose, if necessary, to achieve amenorrhea and relieve symptoms (333).

The significant adverse side effects of *danazol* are related to its androgenic

and hypoestrogenic properties. The most common side effects include weight gain, fluid retention, acne, oily skin, hirsutism, hot flashes, atrophic vaginitis, reduced breast size, reduced libido, fatigue, nausea, muscle cramps, and emotional instability. Deepening of the voice is another potential side effect that is nonreversible. Although *danazol* can cause increased cholesterol and low-density lipoprotein levels and decreased high-density lipoproteins levels, it is unlikely that these short-term effects are clinically important. *Danazol* is contraindicated in patients with liver disease because it is largely metabolized in the liver and may cause hepatocellular damage. *Danazol* is also contraindicated in patients with hypertension, congestive heart failure, or impaired renal function because it can cause fluid retention. The use of danazol is contraindicated in pregnancy because of its androgenic effects on the fetus.

Because the many side effects of oral *danazol* limit its use, alternative routes of administration have been studied. In an uncontrolled pilot study, local *danazol* treatment using a vaginal *danazol* ring (1,500 mg) has been shown to be effective for pain relief in deeply infiltrative endometriosis. This treatment did not cause the classic *danazol* side effects or detectable serum *danazol* levels, and it allowed ovulation and conception to occur (348).

Gonadotropin-releasing Hormone Agonists

Gonadotropin-releasing hormone agonists bind to pituitary GnRH receptors and stimulate LH and FSH synthesis and release. However, the agonists have a much longer biologic half-life (3–8 hours) than endogenous GnRH (3.5 minutes), resulting in the continuous exposure of GnRH receptors to GnRH agonist activity. This exposure causes a loss of pituitary receptors and downregulation of GnRH activity, resulting in low FSH and LH levels. Consequently, ovarian steroid production is suppressed, providing a medically induced and reversible state of pseudomenopause. A direct effect of GnRH agonists on ectopic endometrium is also possible, because expression of the GnRH receptor gene has been documented in ectopic endometrium and because direct inhibition of endometriosis cells has been shown *in vitro* (349). Furthermore, in rat models used to study surgical adhesion formation and endometriosis, GnRH agonist therapy decreased activity of plasminogen activators and matrix MMPs and increased the activity of their inhibitors, suggesting potential GnRH agonist-regulated mechanisms for reducing adhesion formation (350).

Various GnRH agonists have been developed and used in treating endometriosis. These agents include *leuprolide*, *buserelin*, *nafarelin*, *histrelin*, *goserelin*, *deslorelin*, and *triptorelin*. These drugs are inactive orally and must be administered intramuscularly, subcutaneously, or by intranasal absorption. The best therapeutic effect is often associated with an *estradiol* dose of 20 to 40 pg/mL (75–150 pmol/L). These so-called depot formulations are attractive because of the reduced frequency of administration and because nasal administration can be complicated by variations in absorption rates and problems with patient compliance (333). The results with GnRH agonists are similar to those with *danazol* or progestin therapy. **Treatment for 3 months with a GnRH agonist is effective in improving pain for 6 months** (263).

Although GnRH agonists do not have an adverse effect on serum lipids and lipoproteins levels, their side effects are caused by hypoestrogenism and include hot flashes, vaginal

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dryness, reduced libido, and osteoporosis (6%–8% loss in trabecular bone density after 6 months of therapy). Reversibility of bone loss is equivocal and therefore of concern (351,352), especially because treatment periods of longer than 6 months may be required. The goal is to suppress endometriosis and maintain serum estrogen levels of 30 to 45 pg/mL. More extreme estradiol suppression will induce bone loss (351). The dose of daily GnRH agonist can be regulated by monitoring estradiol levels, by the addition of low-dose progestin or estrogen-progestin in an add-back regimen, or by draw-back therapy. **The goal of add-back therapy is to treat endometriosis and endometriosis-associated pain effectively while preventing vasomotor symptoms and bone loss related to the hypoestrogenic state induced by GnRH analogues.** Add-back therapy can be achieved by administering progestins only, including *norethisterone*, 1.2 mg, and *norethindrone acetate*, 5 mg, but bone loss is not prevented by *medrogestone*, 10 mg/day (352,353,354). Add-back therapy can also be achieved by *tibolone*, 2.5 mg/day (353,356) or by an estrogen-progestin combination (i.e., *conjugated estrogens*, 0.625 mg, combined with *medroxyprogesterone acetate*, 2.5 mg, or with *norethindrone acetate*, 5 mg, *estradiol*, 2 mg, and *norethisterone acetate*, 1 mg) (353,354,355,356,357). However, some concern remains about the long-term effects of GnRH analogues on bone loss. In one report, bone mineral

density reduction occurred during long-term GnRH agonist use and was not fully recovered up to 6 years after treatment (358). Use of add-back therapy (2 mg *estradiol* and 1 mg *norethisterone acetate*) did not affect this process (358). Therefore, **GnRH agonists should not be prescribed to girls who have not yet attained their maximal bone density.**

Draw-back therapy has been suggested as an alternative in a study showing that 6 months of intake of 400 µg/day of *nafarelin* was as effective as a draw-back regimen consisting of 1 month of intake of 400 µg/day of *nafarelin* followed by 5 months of 200 µg/day of *nafarelin*, with similar estradiol levels (30 pg/mL) but less loss of bone mineral density (359).

Aromatase Inhibitors

Treatment of rats with induced endometriosis using the nonsteroidal aromatase inhibitor *fadrozole hydrochloride* (360) or *YM511* (361) resulted in a dose-dependent volume reduction of endometriosis transplants. In one case report (362), treatment of severe postmenopausal endometriosis with an aromatase inhibitor, *anastrozole*, 1 mg/day, and elemental *calcium*, 1.5 g/day for 9 months, resulted in hypoestrogenism, pain relief after 2 months, and after 9 months a 10-fold reduction in the 30-mm diameter size of red, polypoid vaginal lesions, along with remodeling to gray tissue. In a pilot study (363), preliminary data were generated suggesting a potential future use of this drug, but randomized controlled trials are needed to confirm these data.

Selective Estrogen Receptor Modulators

In animal models, *raloxifene* therapy resulted in regression of endometriosis. The effect was seen in both a surgically prepared, rat uterine explant model and in Rhesus macaques diagnosed with spontaneous endometriosis before exposure (364).

Efficacy of Medical Treatment

Pain

Medical treatment with progestins, *danazol*, *gestrinone*, or GnRH agonists is effective in treating pain associated with endometriosis, as shown in several prospective, randomized, placebo-controlled double-blind studies (211,250,365,366). Based on published studies, *medroxyprogesterone acetate*, *danazol*, *gestrinone*, and GnRH agonists have similar efficacy in resolution of the laparoscopically documented disease and in pain alleviation (332). **Postoperative medical therapy may be required in patients with**

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incomplete surgical resection and persistent pain. Treatment should be continued at least 3 to 6 months, and pain relief may be of short duration, presumably because endometriosis recurs. Disadvantages of medical therapy over surgical therapy include the high cost of hormone preparations, the high prevalence of side effects, and the higher recurrence rate of endometriosis.

Subfertility

Conception is either impossible or contraindicated during medical treatment of endometriosis. There is no evidence that medical treatment of minimal to mild endometriosis leads to better chances of pregnancy than expectant management (211,280,365,366,367,368,369,370,371).

Adolescent Endometriosis

The incidental finding of minimal to mild endometriosis in a young woman without immediate interest in pregnancy is a common clinical problem. Seventy percent of girls with chronic pelvic pain unresponsive to oral contraceptives or NSAIDs are affected by endometriosis (372). Mild disease can be treated by surgical removal of implants at the time of diagnosis, followed by continuous administration of low-dose combination oral contraceptives to prevent recurrence. More advanced disease can be treated medically for 6 months, followed by continuous oral contraceptives to prevent progression of disease. Gonadotropin-releasing hormone agonists with add-back therapy can be considered for adolescents older than 16 years of age who have completed pubertal maturation (372).

Recurrence

Endometriosis tends to recur unless definitive surgery is performed. The recurrence rate is about 5% to 20% per year, reaching a cumulative rate of 40% after 5 years. The rate of recurrence increases with the stage of disease, the duration of follow-up, and the occurrence of previous surgery (373,374,375,376,377). The likelihood of recurrence appears to be lower when endometriosis is located only on the right side of the pelvis than when the left side is involved (378).

In a recent randomized controlled trial, postoperative low-dose cyclic oral contraceptive use resulted in a significantly lower cumulative recurrence rate after 1 year, but not after 2 to 3 years (271). In women treated with a second operation for recurrent endometriosis, the cumulative recurrence rate was comparable to those rates after laparoscopy or laparotomy (379).

The recurrence rates reported in women 5 years after therapy with various GnRH agonists were 37% for minimal disease and 74% for severe disease (373). In women treated with GnRH agonists or *danazol* for endometriosis associated with pelvic pain, the recurrence rates of endometriosis were similar, and associated pain symptoms usually returned after cessation of therapy (380). **Pain recurs within 5 years in about one in five patients with pelvic pain treated by complete laparoscopic excision of visible endometriotic lesions (381).**

Assisted Reproduction and Endometriosis

The treatment of endometriosis-related infertility is dependent on the age of the woman, the duration of infertility, the stage of endometriosis, the involvement of ovaries, tubes, or both in the endometriosis process, previous therapy, associated pain symptoms, and the priorities of the patient, taking into account her attitude toward the disease, the cost of treatment, her financial means, and the expected results. Assisted reproduction—including controlled ovarian hyperstimulation with intrauterine insemination, IVF, and gamete intrafallopian transfer—may be options for infertility treatment in addition to surgical reconstruction and expectant management. IVF is the method of choice when distortion of the tubo-ovarian anatomy

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contraindicates the use of superovulation with intrauterine insemination or gamete intrafallopian transfer.

Intrauterine Insemination

Endometriosis-associated infertility can be successfully treated with intrauterine insemination, but only if it is done in combination with ovarian stimulation (382). A randomized study (382) compared controlled ovarian hyperstimulation

with FSH and intrauterine insemination with no treatment during 311 cycles in 103 couples with minimal to mild endometriosis as the only infertility factor. In this study, a significantly higher live-birth rate per cycle was reported in the treated group (11%) than in the control group (2%) (OR, 5.6; 95% CI, 1.8–17.4). However, **there is clear evidence that the pregnancy rate in an insemination program is lower in women with endometriosis than in women with unexplained infertility** (383,384). A recent meta-analysis of 5,214 cycles by stepwise logistic regression (385) evaluated the effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility. The odds ratio for pregnancy associated with endometriosis was 0.45 (95% CI, 0.27–0.76) and for male factor was 0.48 (95% CI, 0.37–0.61).

In Vitro Fertilization

Based on several retrospective studies (141,146), investigators have suggested that the pregnancy rate after IVF may be lower in women with endometriosis than in women without the disease. In earlier studies, this finding had been attributed to lower oocyte quality and decreased fertilization rate in women with endometriosis. However, these findings were not confirmed in **more recent studies that reported a normal fertilization rate but a reduced implantation rate per embryo transferred in women obtaining oocytes from donors with endometriosis** (386,387). This reduced implantation rate could be related to increased interleukin-6 levels in follicular fluid of women with endometriosis when compared with controls (388). A more recent case-control study in an IVF egg-donation program compared oocyte receptors in patients with endometriosis stage III or IV (cases) with oocyte receptors in patients without endometriosis (controls). Similar rates of implantation, miscarriage, and pregnancy were observed in cases and controls, suggesting that there is no endometrial implantation problem in women with endometriosis stage III or IV treated with IVF (389). **In another case-control study, the cumulative pregnancy rate and live-birth rates were comparable after five cycles of IVF in women with ovarian endometriosis and those with tubal infertility.** The cumulative pregnancy rates were 63% and 63%, respectively, and the cumulative live-birth rates were 47% and 51%, respectively, but women with ovarian endometriosis had poorer responses and needed higher doses of gonadotropin therapy (390).

When endometriosis was assigned a stage, the pregnancy rate after IVF was decreased in patients with stage IV endometriosis but normal in women with less advanced disease (381,391,392,393,394,395,396). However, some studies have been unable to demonstrate a significant negative correlation between either the presence or stage of endometriosis and the pregnancy rate per cycle (397,398). **The best evidence probably is provided by a recently published meta-analysis (399) showing that IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility, even when women with minimal to mild endometriosis were analyzed separately.** The use of *danazol*, *gestrinone*, or GnRH agonists in women with endometriosis before IVF has been reported to improve the pregnancy rate by some (396,400,401) but not all investigators (398). Prolonged treatment with a GnRH agonist before IVF in moderate to severe endometriosis can be considered and discussed with patients; although improved pregnancy rates have been reported (402,403), the long duration of treatment may limit the practical application of this treatment.

Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma 4 cm or more in diameter is present to confirm the diagnosis histologically. This procedure

may reduce the risk of infection, improve access to follicles, and possibly improve ovarian response (159). The woman should be counseled regarding the risks of reduced ovarian

function after surgery (404) and the loss of the ovary.

Intracytoplasmic Sperm Injection

A recent well-controlled study in patients undergoing intracytoplasmic sperm injection (ICSI) (400) reported a reduced number of oocytes recovered after ovarian aspiration but a normal fertilization rate, implantation rate, and pregnancy rate in women with endometriosis when compared with controls. These normal fertilization, implantation, and pregnancy rates also were reported in another recent study of ICSI (405).

Gamete Intrafallopian Transfer

The use of gamete intrafallopian transfer in patients with endometriosis is reported to result in a higher monthly fecundity rate (25%) than with IVF (14%). This difference may be related to selection bias because less severe forms of endometriosis may have been more likely to be treated with gamete intrafallopian transfer, reserving IVF for more advanced stages of disease (288). In one study, the gamete intrafallopian transfer pregnancy rate in patients with a primary diagnosis of endometriosis (32.5%) was lower than in matched controls (406).

The current evidence suggests that patients with endometriosis have a poorer ovarian response and need a higher dose of gonadotropin therapy in IVF or ICSI programs, but endometrial implantation is not reduced. Future studies evaluating the association between endometriosis and reproductive outcome after assisted reproduction should be prospective and should include the following components (142): .

- Accurate and recent laparoscopic description of the stage of endometriosis.
- Date, number of procedures, and interval between surgical procedures.
- Ultrasonographic evidence of endometriosis, confirmed by cytology or histology when endometriotic cysts are aspirated during oocyte aspiration.
- Effectiveness of interim suppressive therapy between diagnosis and treatment with assisted reproduction.
- Reliability and date of negative diagnosis.
- Clear definition of implantation rate, pregnancy rate, abortion rate, and live-birth rate per started cycle, per oocyte aspiration, and per embryo transfer.

Coping with Disease

Coping with endometriosis as a chronic disease is an important component of management. According to guidelines for the management of endometriosis (159), evidence from two systematic reviews suggests that high frequency transcutaneous electrical nerve stimulation (TENS), acupuncture, vitamin B¹, and magnesium may help to relieve dysmenorrhea (407). Whether such treatments are effective in endometriosis-

associated dysmenorrhea is unknown. Many women with endometriosis report that nutritional and complementary therapies such as reflexology, traditional Chinese medicine, herbal treatments, and homeopathy improve pain symptoms. Although there is no evidence from randomized controlled trials to support the effectiveness of these treatments in endometriosis, they should not be ruled out if the woman feels they work in conjunction with more traditional therapies or that they could be beneficial to her overall pain management and quality of life. Patient self-help groups

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can provide invaluable counseling, support, and advice. The Web site <http://www.endometriosis.org/support.html> provides a comprehensive list of all the self-help groups in the world (159).

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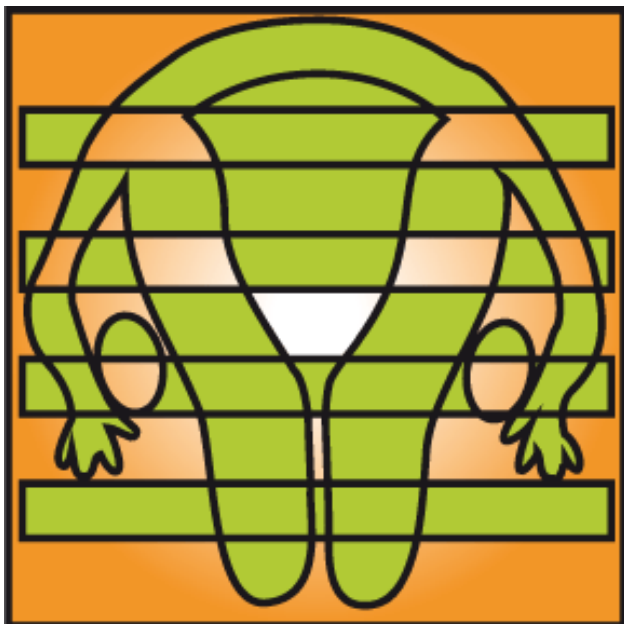
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Infertility

Richard O. Burney

Daniel J. Schust

Mylene W. M. Yao



• **The physician's initial encounter with the infertile couple is the most important one because it sets the tone for subsequent evaluation and treatment. Factors**

from either or both partners may contribute to difficulties in conceiving; therefore, it is important to consider all possible diagnoses before pursuing invasive treatment..

- The main causes of infertility include male factor, decreased ovarian reserve, ovulatory disorders (ovulatory factor), tubal injury, blockage, or paratubal adhesions (including endometriosis with evidence of tubal or peritoneal adhesions), uterine factors, systemic conditions (including infections or chronic diseases such as autoimmune conditions or chronic renal failure), cervical and immunologic factors, and unexplained factors (including endometriosis with no evidence of tubal or peritoneal adhesions)..
- The basic investigations that should be performed before starting any infertility treatment are semen analysis, confirmation of ovulation, and the documentation of tubal patency..
- Male factor is the only cause of infertility in 20% of infertile couples, but it may be a contributing factor in as many as 30% to 40% of cases. Treatment of reversible endocrine or infectious causes of subfertility, such as sexually transmitted diseases and thyroid disorders, tends to be efficacious. Intrauterine insemination (IUI) is the best studied and most widely practiced of all the insemination techniques. Intracytoplasmic sperm injection (ICSI) has allowed couples with male factor infertility to achieve assisted reproductive technology (ART) pregnancy outcomes that are comparable with those of couples with non-male factor infertility using conventional *in vitro* fertilization (IVF) treatment..
- An association between the age of the woman and reduced fertility has been well documented. The decline in fecundability begins in the early 30s and accelerates during the late 30s and early 40s..

Disorders of ovulation account for about 30% to 40% of all cases of female infertility. These disorders are generally among the most easily diagnosed and most treatable causes of infertility..

- **The most common cause of oligo-ovulation and anovulation—both in the general population and among women presenting with infertility—is polycystic ovarian syndrome (PCOS)..**
- **Tubal and peritoneal factors account for 30% to 40% of cases of female infertility. Cervical factor is estimated to be a cause of infertility in no more than 5% of infertile couples. Uterine pathologies constitute the etiologic factor in infertility in as many as 15% of couples seeking treatment and are diagnosed in as many as 50% of infertile patients. Leiomyomas have not been shown to be a direct cause of infertility..**
- **All methods of ART, by definition, involve interventions to retrieve oocytes. These techniques include IVF, ICSI, gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), cryopreserved embryo transfers, and the use of donor oocytes. Because of improved success rates associated with IVF-embryo transfer, the performance of GIFT and ZIFT has declined..**
- **Multiple gestation, especially higher-order multiple gestation, is a serious complication of infertility treatment and has tremendous medical, psychological, social, and financial implications..**
- **Fortunately, recent studies have not shown an increased risk for breast, uterine, or ovarian cancer secondary to medications used for superovulation in the treatment of infertility..**
- **Information on the Society for Assisted Reproductive Technology (SART) and registered ART clinics are accessible by the public at <http://www.sart.org>..**

Infertility is defined as 1 year of unprotected intercourse without pregnancy. This condition may be further classified as *primary infertility*, in which no previous pregnancies have occurred, and *secondary infertility*, in which a prior pregnancy, although not necessarily a live birth, has occurred. *Fecundability* is the probability of achieving pregnancy within a single menstrual cycle, and *fecundity* is the probability of achieving a live birth within a single cycle. The fecundability of a normal couple has been estimated at 20% to 25% (1). On the basis of this estimate, about 90% of couples should conceive after 12 months of unprotected intercourse..

Epidemiology

Infertility affects about 10% to 15% of reproductive-age couples in the United States. Data from the U.S. National Survey of Family Growth indicate that the prevalence of infertility among women who had not been surgically sterilized was 13.3% in 1965, 13.9% in 1982, and 13.7% in 1988 (2). In 1990, about 1 in 3 women in the United States reported 12 consecutive months of unprotected coitus without pregnancy at some time in her life (3). A number of demographic variables, including age and socioeconomic status, have been associated with infertility. As a result of the delay in childbearing in the United States population, more older reproductive-age women are attempting to conceive. **Thus, although the overall prevalence of infertility in the United States has not changed since 1965, the percentage of women with primary infertility has increased significantly.** In 1965, only one of six infertile women was nulliparous, whereas in 1988, more than half of infertile women had never been pregnant (4).

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Although the prevalence of infertility has been stable, the demand for infertility care has increased significantly over the past few decades. Between 1968 and 1984, the number of office visits for infertility increased nearly threefold to 1.6 million visits annually (5). In 1995, it was estimated that about 2% of women (1.2 million) had a medical visit related to their infertility, whereas 13% (7.6 million) had sought medical attention for infertility in their lifetime (6). The increase in the use of infertility medical care stems from many factors, including a heightened awareness that infertility is a medical condition that may be treated in many cases, and sociologic changes that have led to delayed childbearing. Still, despite an increased awareness of available therapies, only 43% of infertile couples seek treatment, and only 24% seek specialized care. Fewer than 2% use *in vitro* fertilization (IVF) or other forms

of assisted reproductive technology (ART) (7). Although infertility is more prevalent among women of relatively low socioeconomic status, patients seeking treatment for infertility are predominantly of high socioeconomic status (4). The women most likely to obtain specialized treatment are 30 years of age or older, white, married, and of relatively high socioeconomic status (7). Familiarity with and access to infertility services among the affluent and better-educated patients probably account for their greater use of these medical resources.

Initial Assessment

The physician's initial encounter with the infertile couple is the most important one because it sets the tone for subsequent evaluation and treatment. The male partner should be present at this first visit because his history is a key component in the selection of diagnostic and therapeutic plans. It cannot be overemphasized that infertility is a problem of the couple. The presence of the male partner, beginning with the initial evaluation, involves him in the therapeutic process. This essential involvement demonstrates that the physician is receptive to the male partner's needs as well as to those of the female partner and allows the male partner an opportunity to ask questions and to voice any concerns.

The physician should obtain a complete medical, surgical, and gynecologic history from the woman. Specifically, information regarding menstrual cyclicity, pelvic pain, and previous pregnancy outcomes is important. Risk factors for infertility, such as a history of pelvic inflammatory disease (PID), intrauterine device use, or pelvic surgery, should be reviewed. A history of intrauterine exposure to *diethylstilbestrol* (DES) is significant. In addition, a review of systems relevant to pituitary, adrenal, and thyroid function is useful. Questions regarding galactorrhea, hirsutism, and changes in weight are particularly relevant. A directed history, including developmental defects such as undescended testes, past genital surgery, infections (including mumps orchitis), previous genital trauma, and medications should be obtained from the male partner. A history of occupational exposures that might affect the reproductive function of either partner is also important, as is information about coital frequency, dyspareunia, and sexual dysfunction. Finally, information should be obtained on any family history of infertility, premature ovarian failure, congenital or developmental defects, mental retardation, and hereditary conditions relevant to preconceptional planning, such as cystic fibrosis, thalassemia, and Tay Sachs disease.

The initial interview provides the physician with the opportunity to assess the

to emphasize the emotional support available to the couple as they proceed with the diagnostic evaluation and suggested treatments. In some cases, referral to a trained social worker or psychologist may be beneficial.

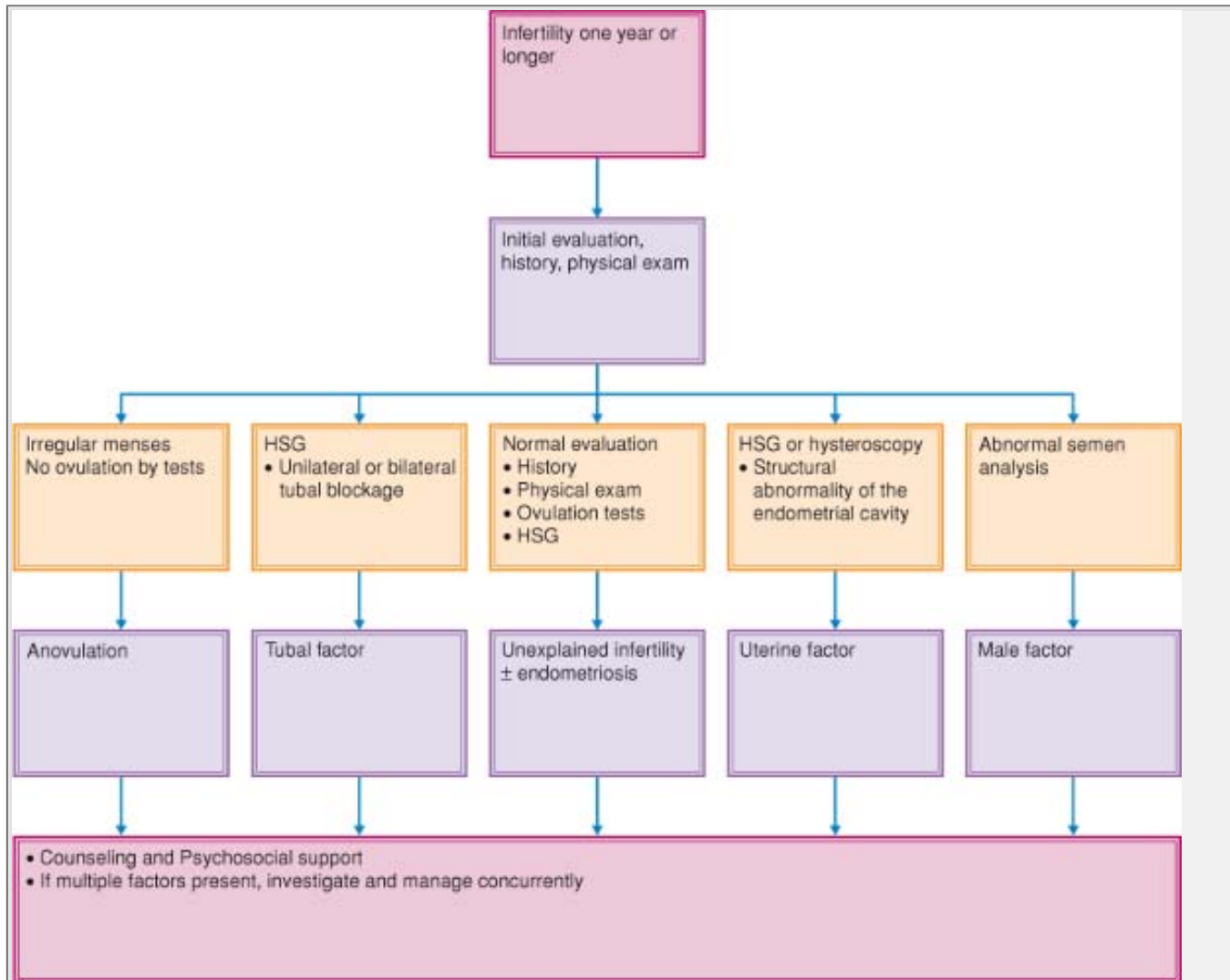


Figure 30.1 Diagnostic and treatment algorithm: infertility. HSG, hysterosalpingography. (From Yao M. Clinical management of infertility. Washington, DC: The Advisory Board: 2000, with permission.)

The physical examination of the woman should be thorough, with particular attention given to height, weight, body habitus, hair distribution, thyroid gland, and pelvic examination. Referral of the man to a urologist for examination often is beneficial if historic information or subsequent evaluation suggests an abnormality. This initial encounter also provides an opportunity to outline the general causes of infertility and to discuss subsequent diagnostic and treatment plans (Figs. 30.1–30.3).

Causes of Infertility

The main causes of infertility include:

- **Male factor.**
- **Decreased ovarian reserve.**
- **Ovulatory disorders (ovulatory factor).**

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- **Tubal injury, blockage, or paratubal adhesions (including endometriosis with evidence of tubal or peritoneal adhesions).**
- **Uterine factors.**
- **Systemic conditions (including infections or chronic diseases such as autoimmune conditions or chronic renal failure).**
- **Cervical and immunologic factors.**
- **Unexplained factors (including endometriosis with no evidence of tubal or**

peritoneal adhesions).

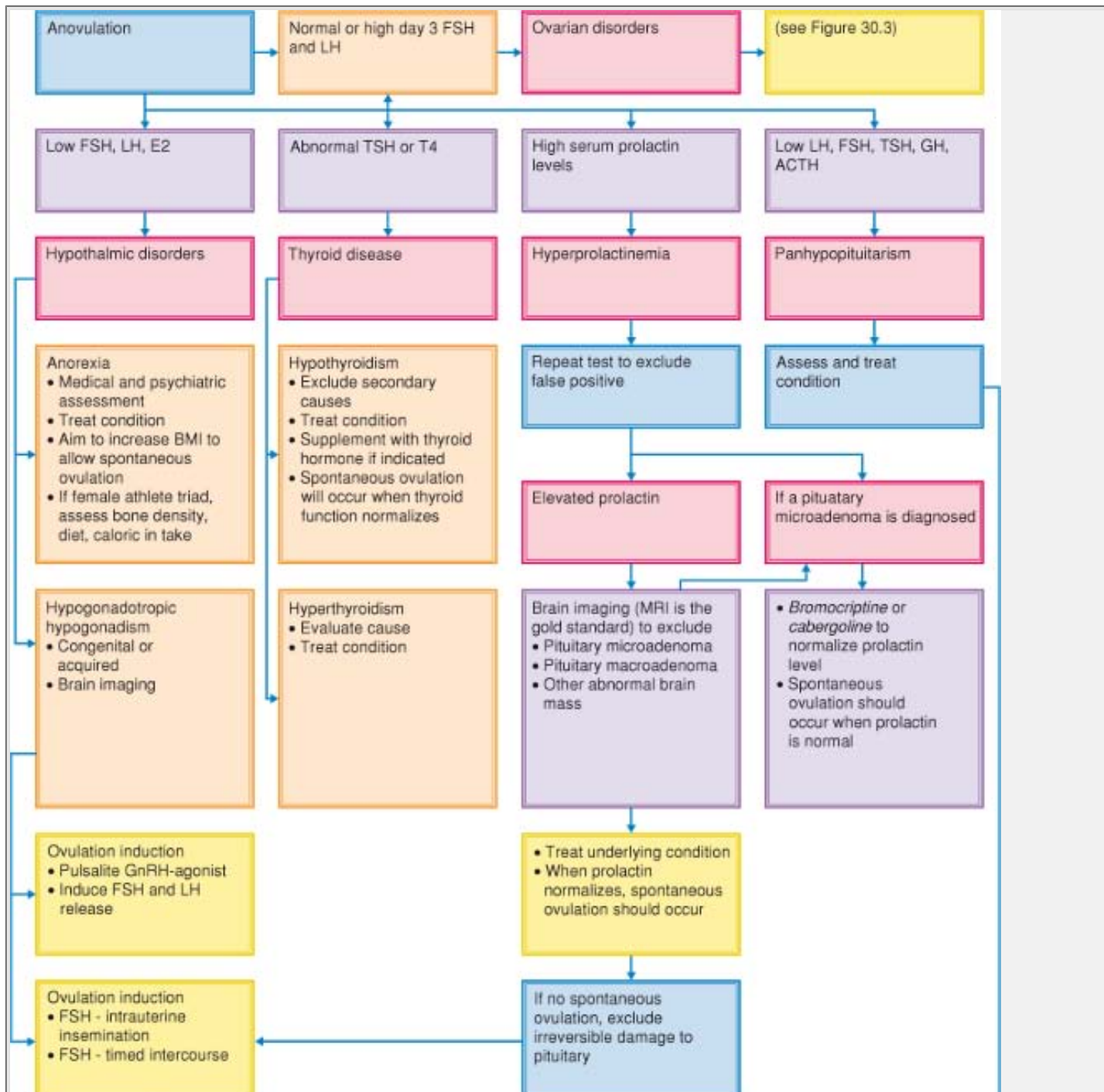


Figure 30.2 Diagnostic and treatment algorithm: anovulation. FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; TSH, thyroid-stimulating hormone; T4, thyroxine; GH, growth hormone; ACTH, adrenocorticotrophic hormone; BMI, body mass index; MRI, magnetic resonance imaging; GnRH, gonadotropin-releasing hormone. (From Yao M. Clinical management of infertility. Washington, DC: The Advisory Board: 2000, with permission.)

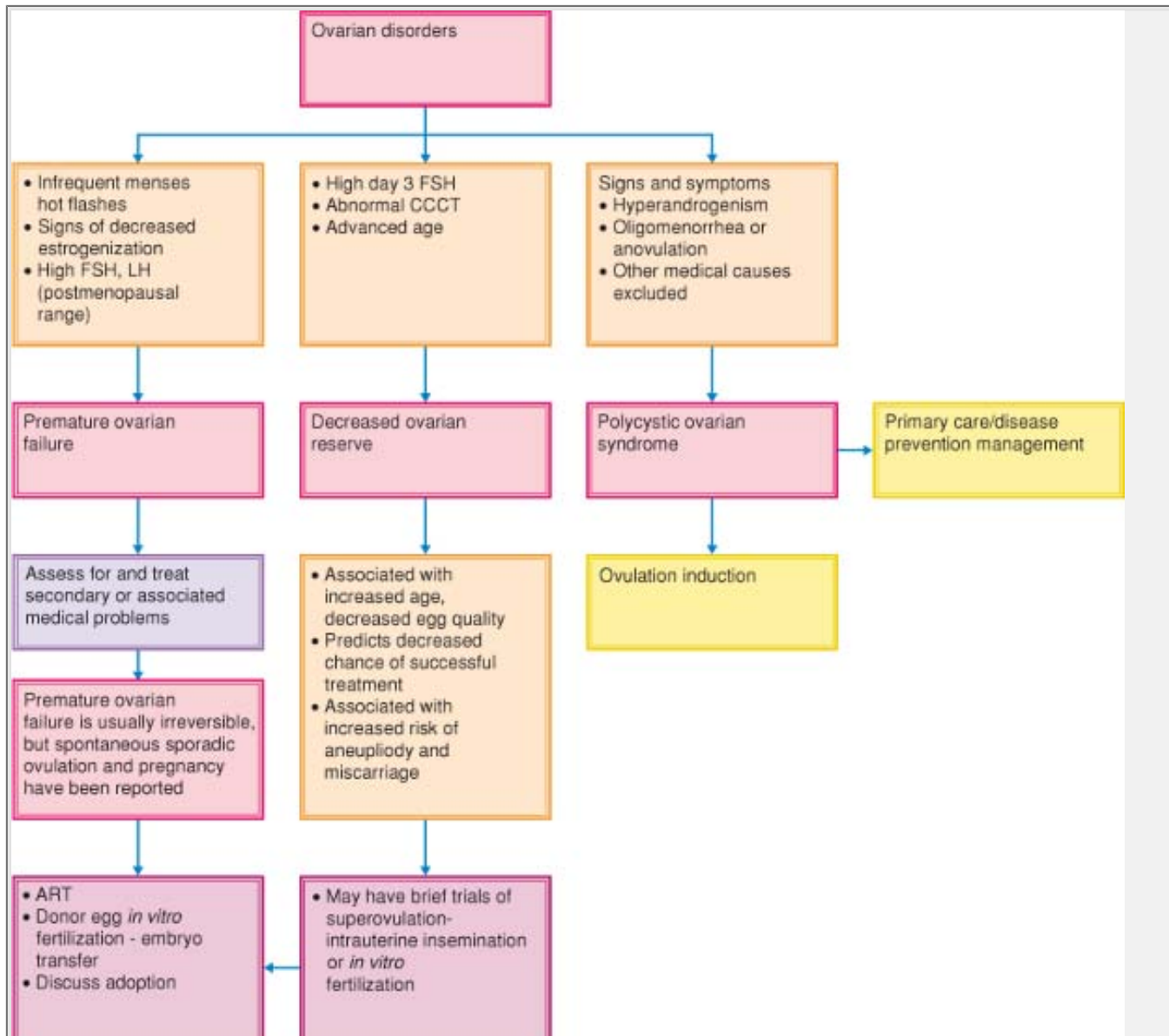


Figure 30.3 Diagnostic and treatment algorithm: ovarian disorders. FSH, follicle-stimulating hormone; LH, luteinizing hormone; CCCT, clomiphene citrate challenge test ART, assisted reproductive technology. (From **Yao M.** Clinical management of infertility. Washington, DC: The Advisory Board: 2000, with permission.)

Factors from either or both partners may contribute to difficulties in conceiving; therefore, it is important to consider all possible diagnoses before pursuing invasive treatment. The relative prevalence of the different causes of infertility varies widely among patient populations (Table 30.1). In many cases, no specific cause is detected despite a thorough evaluation, and the couple's infertility is categorized as unexplained.

Table 30.1 Causes of Infertility

Relative prevalence of the etiologies of infertility (%)	
Male factor	25–40
Both male and female factors	10
Female factor	40–55
Unexplained infertility	10
Approximate prevalence of the causes of infertility in the female (%)	
Ovulatory dysfunction	30–40
Tubal or periotoneal factor	30–40
Unexplained infertility	10–15
Miscellaneous causes	10–15

Very few couples have absolute infertility, which can result from congenital or acquired irreversible loss of functional gametes in either partner or the absence of reproductive structures in either partner. In these specific instances, couples should be counseled regarding their options of adoption, the use of donor gametes, or surrogacy. However, most couples that have difficulty conceiving have subfertility. According to this fundamental concept, most couples could conceive spontaneously in time, but because of known or unidentifiable causes, their spontaneous fecundity rate is so low that medical management is warranted. Another reason to seek medical attention, particularly among

older women, is that as time passes with unsuccessful spontaneous attempts, fecundability will be compromised further by increasing age and concomitantly decreasing ovarian reserve. Although identification of apparent causes of subfertility (such as anovulation or oligospermia) allows treatment to be targeted, effective empiric treatments also greatly increase the chance of a pregnancy even when no distinct cause is identified. Overall, these treatments aim at increasing the probability of conception and implantation by optimizing gamete (sperm and oocyte) and uterine factors.

The basic investigations that should be performed before starting any infertility treatment are semen analysis, confirmation of ovulation, and the documentation of tubal patency. Some treatments, especially ART, are indicated for more than one diagnosis and are discussed in greater detail. Often, more than one cause is identified in a couple. For this reason, multiple approaches to investigation and treatment may be undertaken simultaneously.

Male Factor

Male factor is the only cause of infertility in 20% of infertile couples, but it may be a contributing factor in as many as 30% to 40% of cases (8). However, the combined effects of our increased understanding of genetic causes in male factor infertility and the efficacy of intracytoplasmic sperm injection (ICSI) in ART have revolutionized modern treatment of male factor infertility. For men, semen analysis is inexpensive and noninvasive, and remains fundamental to the infertility evaluation. The value and interpretation of the semen analysis and other tests for male infertility should be considered within the context of male reproductive physiology.

Physiology

The male reproductive tract consists of the testis, epididymis, vas deferens, prostate, seminal vesicles, ejaculatory duct, bulbourethral glands, and urethra. The testes contain two cell types: the Sertoli cells, which line the seminiferous tubules (the site of spermatogenesis), and the Leydig cells (the site of androgen synthesis). In the man, the pituitary gland secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which act on the testes. The former (LH) stimulates the synthesis and secretion of testosterone by the Leydig cells, and the latter (FSH) stimulates the Sertoli cells to secrete inhibin. Both FSH and testosterone act on the seminiferous tubules to stimulate spermatogenesis. In humans,

the development from spermatogonia stem cells to the mature sperm cells takes about 75 days. Spermatogonia undergo mitotic division to give rise to spermatocytes. These spermatocytes subsequently undergo meiosis to produce spermatids, which contain 23 (rather than 46) chromosomes. Upon maturation, spermatids become spermatozoa, which enter the epididymis, where they continue to mature and become progressively more motile during the 12 to 21 days that is required to traverse this tortuous structure.

During ejaculation, mature spermatozoa are released from the vas deferens along with fluid from the prostate, seminal vesicles, and bulbourethral glands. The semen released is a gelatinous mixture of spermatozoa and seminal plasma; however, it thins out 20 to 30 minutes after ejaculation by a process called *liquefaction*. Liquefaction occurs secondary to the presence of proteolytic enzymes within the prostatic fluid. The released spermatozoa are not usually capable of fertilization. Instead, a series of complex biochemical and electrical events, termed *capacitation*, must take place within the sperm's outer surface membrane before fertilization can occur. Normally, capacitation occurs in the cervical mucus; however, it can occur in physiologic media *in vitro*. Finally, as part of fertilization, the sperm must undergo the acrosome reaction, in which the release of enzymes of the inner acrosomal membrane results in the breakdown of the outer plasma membrane and its fusion with the outer acrosomal membrane (9). The acrosome reaction and binding of sperm and ovum surface proteins are important for the penetration of the ovum's zona pellucida and subsequent fusion between the ovum and sperm. As the sperm penetrates the egg, it initiates a hardening of the zona pellucida (cortical reaction), which prevents penetration by additional sperm (9,10).

The concept of a global decline in sperm counts needs to be reassessed (11,12). A number of recent analyses reported no decrease in sperm counts over time (13,14,15). Geographic differences in the results of semen analyses do seem to exist, but a global trend toward decreasing semen quality does not (16,17,18). Furthermore, the rate of male factor infertility has not increased significantly in recent decades. Thus, even if semen characteristics are changing, these changes do not appear to be having a dramatic clinical effect. Nevertheless, exposures to environmental toxins may certainly be harmful to sperm, and the incidence of some exposures (e.g., phytoestrogens) may be on the rise. Marijuana and cocaine use can reduce sperm concentration (19,20). Certain drugs may reduce sperm count or function or cause ejaculatory dysfunction (Table 30.2). Finally, **consumption of**

caffeine, alcohol, and smoking has been associated with diminished semen quality or fecundity in a dose-related fashion (21,22).

Table 30.2 Drugs that Can Impair Male Fertility

Impaired spermatogenesis— *sulfasalazine, methotrexate, nitrofurantoin, colchicine, chemotherapy*

Pituitary suppression— *testosterone injections, gonadotrophin-releasing hormone analogues*

Antiandrogenic effects— *cimetidine, spironolactone*

Ejaculation failure— *α blockers, antidepressants, phenothiazines*

Erectile dysfunction— *β blockers, thiazide diuretics, metoclopramide*

Drugs of misuse— *β anabolic steroids, cannabis, heroin, cocaine*

From **Hirsh A**. Male infertility. *BMJ* 2003;327:669–672, with permission.

Semen Analysis

The basic semen analysis measures **semen volume, sperm concentration, sperm motility, and sperm morphology**. In addition, many laboratories measure pH, fructose levels, and white blood cell counts within the semen. Normal values suggested by the World Health Organization (WHO) are listed in Table 30.3 (23). These values represent only general guidelines, and normal values should be established by individual andrology laboratories.

Specimen Collection

The method used for semen specimen collection is important to the achievement of accurate results. **The optimal period of abstinence before semen collection is unknown; however, because a decrease in sperm concentration is associated with frequent ejaculation, a period of 2 to 3 days usually is recommended.** The specimen should be obtained by masturbation and collected in a clean container. Because of the presence of spermicidal agents, collection into condoms is generally unacceptable, although special sheaths that do not contain spermicides are available for semen collection. All semen specimens should be kept at body temperature and taken to the laboratory within one-half to one hour of collection. Even when the specimen is obtained under optimal circumstances, interpretation of the results of the semen analysis is complicated by variability within the same individual, wide differences in normal semen parameters, and their relativity to

the minimum parameters required for conception (11). Semen parameters also may vary widely from one man to another and among men with proven fertility. In many circumstances, several specimens are necessary to verify an abnormality.

Table 30.3 Semen Analysis Terminology and Normal Values

Semen analysis terminology

Normozoospermia—all semen parameters normal

Oligozoospermia—reduced sperm numbers

Mild to moderate: 5–20 million/mL of semen

Severe: <5 million/mL of semen

Asthenozoospermia—reduced sperm motility

Teratozoospermia—increased abnormal forms of sperm

Oligoasthenoteratozoospermia—sperm variables all subnormal

Azoospermia—no sperm in semen

Aspermia (anejaculation)—no ejaculate (ejaculation failure)

Leucocytospermia—increased white cells in semen

Necrozoospermia—all sperm are non-viable or non-motile

Normal seminal fluid analysis (World Health Organization, 2002)

Volume>2 mL

Sperm concentration>20 million/mL

Sperm motility>50% progressive or >25% rapidly progressive

Morphology (strict criteria)>15% normal forms

White blood cells>1 million/mL

Immunobead or mixed antiglobulin reaction testa <10% coated

^aTests for the presence of antibodies coating the sperm

From **Hirsh A**. Male infertility. *BMJ* 2003;327:669–672, with permission.

Sperm Volume

The normal ejaculated volume of semen is 1.5 to 5 mL. Volumes may be abnormally low in cases of retrograde ejaculation, and high volumes usually reflect relatively long periods

of abstinence or inflammation of the accessory glands. Absence of fructose or high pH may be associated with ejaculatory tract obstruction or seminal vesicle dysfunction.

Sperm Concentration

Sperm concentration or density is defined as the number of sperm per milliliter in the total ejaculate. Establishing a lower limit of normal for sperm concentration is difficult.

Historically, cutoffs of 60 million sperm per milliliter for normal fertility have been advocated, but most WHO laboratories recognize the value of 20 million sperm per milliliter as a lower limit of normal (24).

Sperm Motility

An equally important parameter in the semen analysis is sperm motility, which is defined as the percentage of progressively motile sperm in the ejaculate. Lower limits of normal vary considerably and depend on the local laboratory's experience. A reduction in sperm motility is referred to as *asthenozoospermia*. The WHO and many laboratories use a cutoff of 50% motility as the lower limit of normal, whereas others use less than 40% motility as a criterion for defining asthenospermia (25). Computer-assisted semen analysis, in which computer-generated images of sperm specimens quantitate both sperm counts and sperm motility, may yield results very different from those of nonautomated semen analyses. Regardless of how motility is assessed, the interpretation of sperm motility—as with sperm concentration—is hampered by both significant variability among repeat samples obtained from a single individual and poor correlation between values for normal motility and fertility potential.

Sperm Morphology

An abnormality of sperm morphology is known as *teratozoospermia*. The WHO uses a fairly permissive visual assessment of sperm within a semen specimen to assess morphology value, with greater than 30% normal forms defined as acceptable. More stringent criteria have evolved from other sources. **The strict Tygerberg criteria were introduced by Kruger et al. in 1986 to assess sperm morphology (26).** Using this system, the entire spermatozoon—including the head, midpiece, and tail—is assessed, and even mild abnormalities in head forms are classified as abnormal. Most sperm from normal men exhibit minor abnormalities when subjected to Tygerberg standards. One advantage of these strict criteria, however, is that the Tygerberg classification correlates with prognosis in

IVF treatment. For example, greater than 14% normal morphology is associated with normal rates of fertilization in IVF programs; 4% to 14% normal morphology is associated with a "good prognosis." Values of less than 4% normal sperm morphology are associated with poor prognosis for fertilization and pregnancy in IVF (27). In some studies, this sperm morphology classification has also been found to be predictive of pregnancy outcomes after intrauterine insemination (IUI) treatment, especially when the total motile sperm count is less than 1×10^6 (23). The disparity in criteria for assessment of semen morphology mandates that to interpret semen analysis results properly, the clinician must thoroughly understand the methodology used by the local andrology laboratory.

White Blood Cells

Although measurements of semen volume, sperm concentration, sperm motility, and sperm morphology make up the standard semen analysis, some laboratories also report numbers of round cells. These cells, which may be lymphocytes, can signify the presence of prostatitis or, alternatively, may actually be immature germ cells.

These two cell types can be distinguished by an immunoperoxidase–staining technique that identifies leukocytes (Endtz test) (28). The WHO views ejaculates with more than 5 million round cells per milliliter or more than 1 million leukocytes per milliliter as abnormal (29).

However, the prognostic significance of leukocytes in the semen is controversial. The presence of immature sperm cells in the ejaculate suggests a defect in spermatogenesis and, therefore, may signify a relatively poor prognosis for fertilization (30).

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Although the standard semen analysis and associated tests provide a fairly reasonable picture of semen quality, they yield little information about sperm function. These specialized tests may be pursued to assess sperm viability, fertilization potential (zona–free hamster oocyte test), the presence of antisperm antibodies, and the effect of cervical mucus on sperm viability and function (postcoital test). In general, these tests are not currently considered part of the standard assessment because their prognostic value and impact on management are limited by poor specificity, poor reproducibility, or controversial interpretation of the results (31,32).

Further Evaluation

If abnormalities in the semen are detected, further evaluation of the male partner by a urologist is indicated to diagnose the defect (31). Table 30.4 lists the differential diagnoses for male factor infertility (33). Several groups have attempted to assess the distribution of male infertility diagnoses; two such distributions are shown in Table 30.5 (34,35). The first is the result of a WHO study of 7,057 men with complete diagnoses based on the WHO standard investigation of the infertile couple (35). The figures include data from cases in which the male partner was normal and the presumed

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cause of the couple's infertility was a female factor. The second distribution is the result of a study of 425 subfertile male patients (34). Although the two studies represent different populations (one is from a study of couples, the other from a urologic practice) and differ in their distribution of male infertility diagnoses, idiopathic male factor and varicocele predominate. Other anatomic and endocrine causes occur less frequently.

<i>Pretesticular</i>	<i>Testicular</i>
<i>Endocrine</i>	<i>Genetic</i>
Hypogonadotropic hypogonadism	Klinefelter's syndrome
<i>Coital disorders</i>	Y chromosome deletions
Erectile dysfunction	Immotile cilia syndrome
Psychosexual	<i>Congenital</i>
Endocrine, neural, or vascular	Cryptorchidism
Ejaculatory failure	<i>Infective (orchitis)</i>
Psychosexual	<i>Antispermatogetic agents</i>
After genitourinary surgery	Heat
Neural	Chemotherapy
Drug related	Drugs
<i>Posttesticular</i>	Irradiation
<i>Obstructive</i>	<i>Vascular</i>
Epididymal	Torsion
Congenital	Varicocele
Infective	<i>Immunologic</i>

Vasal	<i>Idiopathic</i>
Genetic: cystic fibrosis	
Acquired: vasectomy	
<i>Epididymal hostility</i>	
Epididymal asthenozoospermia	
<i>Accessory gland infection</i>	
<i>Immunologic</i>	
Idiopathic	
Postvasectomy	

From **De Kretser DM**. Male infertility. *Lancet* 1997; 349: 787–790, with permission.

<i>Cause</i>	<i>Percentage</i>	<i>Cause</i>	<i>Percentage</i>
No demonstrable cause	48.5	Varicocele	37.4
Idiopathic abnormal semen	26.4	Idiopathic	25.4
Varicocele	12.3	Testicular failure	9.4
Infectious factors	6.6	Obstruction	6.1
Immunologic factors	3.1	Cryptorchidism	6.1
Other acquired factors	2.6	Low semen volume	4.7
Congenital factors	2.1	Semen agglutination	3.1
Sexual factors	1.7	Semen viscosity	1.9
Endocrine disturbances	0.6	Other	5.9
Total	103.9^a		100

^a More than 100% because of multiple factors.

From **The ESHRE CAPRI Workshop Group**. Male sterility and subfertility: guidelines for management. *Hum Reprod* 1994; 9: 1260–1264, and **Burkman LJ, Cobbington CC, Franken DR, et al**. The hemizona assay (HZA): development of a diagnostic test for the binding of human spermatozoa to the human hemizona pellucida to predict fertilization potential. *Fertil Steril* 1988; 49: 688–697, with permission.

Treatment

Significant deviations from the normal range of sperm count, concentration, motility, and morphology indicate the presence of male factor infertility. Treatment of male factor infertility may be classified as medical, surgical, or ART-related therapies. The diagnosis and treatment of azoospermia (no sperm on semen analysis) will be discussed separately from other forms of male factor infertility.

Treatment of reversible endocrine or infectious causes of subfertility, such as sexually transmitted diseases and thyroid disorders, tends to be efficacious.

However, medical therapies for other causes of male factor infertility are severely limited. *Clomiphene citrate*, an estrogen agonist and partial antagonist, has often been used to treat male infertility of idiopathic origin. *Clomiphene citrate* acts on the hypothalamic-pituitary axis and, in men, increases serum levels of LH, FSH, and testosterone (36). Most studies have shown that *clomiphene citrate* treatment yields little improvement in semen parameters and no improvement in pregnancy rates (37), whereas treatment with pure FSH during ART has resulted in significant increases in fertilization rates (38).

Varicocele

A varicocele is an abnormal dilation of the veins within the spermatic cord.

Varicoceles nearly always occur on the left side, presumably because of the direct insertion of the spermatic vein into the renal vein on that side.

The pathophysiologic effects of varicocele on testicular function are uncertain but appear to be mediated by an associated rise in testicular temperature or a reflux of toxic metabolites from the left adrenal or renal veins (39). In either event, the effect on sperm production is bilateral. Understanding of the role of varicoceles in infertility is complicated by the prevalence of varicoceles in fertile men and the efficacy of varicocele repair in infertile men.

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One WHO study found varicocele to be present in 25.4% of men with abnormal semen analyses, as opposed to 11.7% of men with normal semen (40). This study failed to demonstrate a difference in the frequency of spontaneous pregnancies among couples in which the men had varicoceles versus those who did not. When compared with fertile men with or without varicoceles, however, infertile patients with varicoceles have higher levels of FSH, smaller testes, and lower sperm concentration and motility (41).

Varicocele repair, which involves interruption of the internal spermatic vein, is commonly performed in the 40% of infertile men with clinically evident varicoceles. Currently, it is

performed as an outpatient procedure and may involve laparoscopy, open surgery, or the injection of embolizing agents. **Despite its widespread use, the therapeutic benefits of varicocele repair remain controversial.** Two multicenter trials have shown that pregnancy rates are significantly increased after varicocelectomy (42,43). However, the validity of the control groups in each of these trials has been criticized (44). A more recent meta-analysis of four randomized, controlled trials involving a total of 385 patients failed to demonstrate significantly altered pregnancy rates after varicocelectomy (44,45,46,47,48).

Artificial Insemination

Artificial insemination encompasses a variety of procedures. All involve the placement of whole semen or processed sperm into the female reproductive tract, which permits sperm-ovum interaction in the absence of intercourse. The placement of whole semen into the vagina as a mode of fertility treatment is now rarely performed except in cases of severe coital dysfunction. Currently, all of the common forms of artificial insemination involve processed sperm obtained from the male partner or a donor. **Artificial insemination has mainly been used to treat unexplained infertility (usually combined with superovulation) and male factor infertility.** The efficacy of each type of insemination method should be assessed separately for each of these two diagnoses.

Types of Insemination for Unexplained Infertility

Many techniques for artificial insemination have been described, but only intracervical and intrauterine insemination have been routinely employed. **Intrauterine insemination is the best studied and most widely practiced of all the insemination techniques.** It involves placement of about 0.3 to 0.5 mL of washed, processed, and concentrated sperm into the intrauterine cavity by transcervical catheterization. In contrast with IUI, intracervical insemination may be performed either with unwashed or with processed specimens. The success rates with intracervical insemination are consistently lower than those with IUI and are further discussed under "Unexplained Infertility" (49).

Processing Semen

Two important issues regarding the use of artificial insemination procedures are the mode of semen processing and the number and timing of inseminations. Many protocols have been developed for sperm preparation. Seminal fluid usually is prevented

from reaching the intrauterine cavity and intra-abdominal space by the cervical barrier. The introduction of seminal fluid past this barrier may be associated with severe uterine cramping or anaphylactoid reactions, possibly mediated by seminal factors such as prostaglandins. Thus, protocols for processing whole semen include the washing of specimens to remove seminal factors and to isolate pure sperm. Some semen preparation methods attempt to further enhance sperm motility or morphology by using additional separation protocols. These methods include centrifugation through density gradients, sperm migration protocols, and differential adherence procedures. Finally, phosphodiesterase inhibitors, such as pentoxifylline, have been used during semen processing in an attempt to enhance sperm motility, fertilization capacity, and acrosome reactivity for IVF procedures (50).

Intrauterine Insemination as Treatment for Male Factor Infertility

Studies of the efficacy of IUI in the treatment of male factor infertility have been difficult to assess

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because of variations in inclusion criteria and the limitations of sperm function tests. Considering these limitations, **the benefits of IUI in male factor infertility have been accepted because IUI appears to result in higher pregnancy rates than natural intercourse or intracervical insemination (OR 2.20, 95% CI, 1.43–3.39) (51). However, the IUI pregnancy rates are generally lower in couples with male factor infertility than in couples with unexplained infertility (4.8% versus 11.6%) (51).** A retrospective analysis of 1,841 couples undergoing 4,056 cycles of IUI for male factor infertility found that pregnancy rates were related to total motile sperm count. Optimal pregnancy rates (>8.2% per cycle) were reached with initial total motile sperm counts of greater than or equal to 5.0×10^6 . Higher counts did not necessarily yield higher pregnancy rates. The minimal total motile sperm count that resulted in a pregnancy was 1.6×10^6 (52). Some couples with male factor infertility do not achieve pregnancy with artificial insemination, whereas others have initial semen parameters that make insemination a suboptimal approach. In these couples, the use of ART, especially with ICSI, may be superior treatment options. Because ICSI is highly effective and requires only that viable sperm be present, almost all cases of male factor infertility can be treated successfully. Because the IUI success rates are extremely low if the total motile sperm count is less than 0.5×10^6 , ICSI should be considered in such cases (53). Finally, ICSI should be recommended after a maximum of three IUI cycles have failed in a couple with male factor infertility.

Azoospermia: Classification and Treatment

Azoospermia is the absence of spermatozoa in the ejaculate. Azoospermia is found on semen analysis in about 5% of all couples being investigated for infertility (54), and its incidence is 1% in all men and 10% to 15% among infertile men (55,56).

The classification of azoospermia reflects the etiology, prognosis, and treatment and differentiates the causes as pretesticular, testicular, and posttesticular (57).

Pretesticular Azoospermia

Pretesticular azoospermia represents those conditions in which the hypothalamic– pituitary axis fails to stimulate spermatogenesis within the testis. Congenital, acquired, and idiopathic etiologies of hypogonadotropic hypogonadism are included in this category. A full endocrine history, including information on puberty and growth and a review of endocrine systems, should guide the physician in the evaluation of the patient with hypogonadotropic hypogonadism. Laboratory investigations of particular benefit in this population include measurement of serum LH, FSH, testosterone, and prolactin levels and imaging of the pituitary gland. Low levels of gonadotropins (LH and FSH) and low serum levels of testosterone are characteristic of hypogonadotropic hypogonadism.

Hormonal treatment of hypogonadotropic hypogonadism is effective. Administration of pulsatile *gonadotropin-releasing hormone* (GnRH) therapy is both conceptually indicated and effective in infertile men with hypothalamic dysfunction (58), including those patients with Kallmann syndrome. Infertile males with hypogonadotropic hypogonadism secondary to panhypopituitarism also may respond to GnRH therapy (59). An alternative treatment uses *human chorionic gonadotropin* (hCG), 1,000–2,500 IU twice a week, with the dose titrated to maintain serum testosterone and estradiol levels within the normal range. Treatment with hCG is then combined with *human menopausal gonadotropin* (hMG), which is given at a dose of 150 IU three times weekly (60,61). Spermatogenesis and pregnancy can be achieved in as many as 80% to 88% of patients after 1 year of therapy (60,61).

Testicular Azoospermia

Gonadal failure is the hallmark of testicular azoospermia. Causes of this condition may be congenital or genetic (e.g., Klinefelter syndrome, microdeletion of Y chromosome), acquired (e.g., radiation therapy, chemotherapy, testicular torsion, or mumps orchitis), or

developmental (e.g., testicular maldescent). The latter disorder may be associated most closely with male factor infertility in the absence of complete testicular azoospermia. A large observational cohort study suggested that infertility was, in fact, associated with congenital bilaterally maldescended testes, but that men with congenital unilaterally maldescended testes did not have decreased fertility when compared with controls (62).

Men with hypergonadotropic hypogonadism (elevated levels of LH and FSH with low serum levels of testosterone) **generally have primary gonadal failure**. A karyotype should be obtained in such cases to detect chromosomal abnormalities such as *Klinefelter syndrome* (47,XXY). Acquired causes of primary gonadal failure are usually evident based on the history, but the diagnosis should be confirmed by assessment of the serum hormonal profile and biopsy. If the diagnosis of gonadal failure is confirmed on biopsy, endocrine therapy is contraindicated.

It is becoming increasingly evident that some cases of male factor infertility that have previously been categorized as idiopathic are actually the result of genetic defects on the Y chromosome (Table 30.6). The two most commonly implicated candidate gene families are the RNA-binding motif (*RBM*) and the "deleted in azoospermia" (*DAZ*) families, but microdeletions at various loci on the Y chromosome have been described. For example, microdeletions in Yq11.23 can occur in one or more of three regions: *AZFa* (proximal), *AZFb* (central), and *AZFc* (distal). Microdeletions in the Y chromosome have been identified in 10% to 20% of men with idiopathic azoospermia or severe oligospermia (63,64) and in 7% of 200 infertile men (65). Semen analyses in affected men varied between oligospermia and azoospermia. Microdeletions in the Y chromosome occur in 2% of fertile men. These microdeletions can be transmitted to the male offspring, who may then suffer from infertility. Therefore, screening for genetic causes is indicated in nonacquired cases of testicular azoospermia so that genetic counseling can be provided before treatment. Testicular azoospermia is treated by surgical retrieval of spermatozoa with subsequent fertilization of the oocyte by ICSI.

Intracytoplasmic Sperm Injection

This micromanipulation technique is performed to increase the fertilization rate of oocytes retrieved during ART by direct injection of a live sperm into the oocyte, thereby theoretically bypassing limitations imposed by sperm motility, defective capacitation or acrosome reaction, and sperm binding the zona pellucida.

This technique was first reported to result in human pregnancies in 1992 (66). The

procedure involves stripping the aspirated cumulus complex of all

surrounding granulosa cells so that micromanipulation can be performed on the egg itself. A viable sperm is then inserted into the cytoplasm of the egg (ooplasm).

<i>Clinical diagnosis</i>	<i>Genetic tests</i>	<i>Most common defects</i>	<i>Incidence (%)</i>
Congenital bilateral absence of vas deferens (CBAVD)	Cystic fibrosis (CFTR gene)	ΔF508, R117H	66
Non-obstructive azoospermia	Karyotype	47, XXY AZFa, AZFb ^a , AZFc	15–30 10–15
Severe (<5M/mL) oligozoospermia	Karyotype Y chromosome microdeletions	47, XXY Translocation Partial AZFb, AZFc	1–2 0.2–0.4 7–10

CFTR = cystic fibrosis transmembrane conductance regulator; AZF, azoospermia factor; ^aAZFb the most severe (DAZ gene—deleted in azoospermia) causes the most severe defects of spermatogenesis; AZFc causes the mildest defects of spermatogenesis
From **Hirsh A**. Male infertility. *BMJ* 2003;327:669–672, with permission.

In general, ICSI has allowed couples with male factor infertility to achieve ART pregnancy outcomes that are comparable with those of couples with non-male factor infertility using conventional IVF treatment. The indications of ICSI have evolved since its introduction and will continue to evolve as more is learned about its risks and benefits. One absolute indication for ICSI is severe male factor infertility as demonstrated by total progressively motile sperm counts ($0.5 \times 10^6/\text{mL}$ and $<3\%$ normal morphology according to strict Tygerberg criteria) (53). Sperm counts of less than $0.5 \times 10^6/\text{mL}$ are associated with poor fertilization rates in IVF, and this finding alone is also an indication for ICSI (67). Other indications for ICSI include the sole presence of spermatozoa lacking an acrosome or those that are completely immotile, as well as the use of surgically recovered epididymal or testicular sperm. Other absolute indications for ICSI are non-male factor-related and include a history of fertilization failure with conventional IVF and the fertilization of oocytes

before preimplantation genetic diagnosis (68). The benefit of combined IVF/ICSI in ART for unexplained infertility also is described under "Unexplained Infertility."

Micromanipulation is a highly skilled technique. When performed by specially trained embryologists, the immediate risk for damaging the manipulated oocyte is less than 10% (53). Because the particular spermatazoa used for ICSI might otherwise be incapable of fertilization, concerns have been voiced regarding possible increased risks for congenital abnormalities among ICSI offspring. Several large series have followed 1,987, 1,139, and 730 children born after ICSI (69). Each has reported no increase in major or minor congenital malformations among offspring produced by ICSI when compared with the general population (69,70,71) and when adjusted for multiple gestation (70). However, an increased incidence of sex chromosome karyotypic abnormalities (69,72) and hypospadias (70) has been suggested. Because the prevalence of sex chromosome karyotypic abnormalities and other genetic factors is increased in infertile men with severe oligospermia or azoospermia, genetic counseling should be offered before treatment with ART (73).

Posttesticular Azoospermia

In posttesticular azoospermia, the hypothalamic–pituitary axis and spermatogenesis are normal. No sperm appear in the ejaculate secondary to congenital absence or obstruction of the vas deferens or ejaculatory ducts, acquired obstruction of these ducts, or ductal dysfunctions, including retrograde ejaculation. Although low seminal pH (6.7–8.0) or low seminal fructose may signal the congenital absence or obstruction of the vas deferens, the diagnosis is confirmed by vasography. In some cases, testicular biopsy may be indicated to differentiate between primary testicular damage and outflow obstruction. Congenital bilateral absence of the vas deferens (CBAVD) is found in 1% to 2% of infertile men and 95% of men with cystic fibrosis (74). Common mutations of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), which encodes a cyclic adenosine monophosphate (cAMP)–regulated chloride channel, can be found in some infertile men with CBAVD, despite the absence of clinical symptoms of cystic fibrosis. Therefore, screening for mutations in the *CFTR* gene is indicated if men with CBAVD plan to undergo sperm retrieval and ICSI to conceive using their own sperm. One cost–effective screening method addressing this problem involves screening the female partner for the three most common mutations in the *CFTR* gene. If negative, the couple has a risk of less than 1 in 1,500 for conceiving a child with cystic fibrosis, regardless of the paternal genotype (33).

Prior vasectomy is probably the most common cause of posttesticular azoospermia

one study, vas deferens patency was obtained in 86% of cases, and pregnancy was

achieved in 52% of cases after primary procedures (75). Rates of patency and pregnancy vary inversely with the length of time from vasectomy. For those patients with azoospermia 3 months after the reversal procedure, either the reanastomosis has failed or the epididymis is obstructed. However, repeat vasovasostomy is associated with patency rates of 75% and pregnancy rates of 43% (75).

Epididymal obstruction is diagnosed by finding normal spermatogenesis on testicular biopsy. Vasography can be used to determine the level of obstruction, but because of its risk of increased scarring, it is done only if reconstructive surgery is performed with the procedure. Alternatively, transrectal ultrasonography (TRUS) findings, in conjunction with the presence of large numbers of sperm in the seminal vesicle aspiration, strongly suggest ejaculatory duct obstruction without the high risk of scarring (76).

There are two approaches to the treatment of posttesticular obstruction if the use of donor sperm is not being considered. Epididymal aspiration proximal to the obstruction may be used to obtain sperm for use in ART in cases of epididymal or vas deferens obstruction. Alternatively, microsurgical vasoepididymostomy is associated with patency rates of 70% and postoperative pregnancy rates of 44% at 1 year if no other infertility factor is present (77).

Some men with reduced semen volume may have **retrograde ejaculation**, in which sperm is propelled into the bladder during ejaculation rather than through the urethra. **This diagnosis can be confirmed by examination of a urine specimen that is obtained by voiding after ejaculation or catheterization.** This condition occurs in rare cases of patients with diabetes mellitus, in certain neurologic conditions, and after bladder or prostatic surgery. For subfertile men with retrograde ejaculatory dysfunction, α -adrenergic agonists such as *phenylephrine* have been reported to strengthen internal urethral sphincter tone (78). Sperm may also be isolated from the neutralized urine of men with retrograde ejaculation and processed for insemination or for ART (79).

Surgical Sperm Recovery for Intracytoplasmic Sperm Injection

Among the many surgical methods for sperm recovery, the most widely described

are **microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), testicular sperm extraction (TESE), and percutaneous testicular sperm fine-needle aspiration (TESA, also called *fine-needle aspiration*, or FNA)** (80). The choice of surgical sperm recovery method depends on the underlying diagnosis, whether the goal of the procedure is diagnostic or therapeutic, and whether isolated sperm will be used immediately or will be cryopreserved.

In cases of posttesticular azoospermia, in which spermatogenesis is expected to be normal, all four methods give successful sperm recovery greater than 90% (81). Both MESA and TESE are open surgical procedures performed with an operating microscope and general or regional anesthesia, whereas TESA and PESA are noninvasive, blind aspiration procedures that are performed with 19- to 21-gauge needles. Alternatively, a 14-gauge Trucut needle, which gives a higher sperm yield, can be used in these procedures (82). Because MESA allows for diagnosis and possibly reconstruction, and usually yields very large numbers of sperm, cryopreservation and avoidance of repeat surgery may be possible (83). Although PESA and TESA appear less invasive, there is increased risk of bleeding, epididymal injury, and postsurgical fibrosis, which can lead to failure of sperm recovery in repeat procedures (84,85).

A meta-analysis found no difference in the rates of fertilization, implantation, or ongoing pregnancy between epididymal and testicular sperm for patients with the same diagnosis (86). Fertilization and implantation rates have been reported to be similar in a retrospective analysis comparing TESA with open biopsy using TESE (81). Further, cryopreservation of spermatozoa within testicular tissues for use in subsequent ICSI treatment

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cycles has been reported (87). Fresh and frozen-thawed epididymal (88) or testicular spermatozoa (89) appear to have comparable fertilization and ongoing pregnancy rates when used for ICSI.

In contrast to posttesticular azoospermia, patients with testicular azoospermia require the use of TESE or TESA, and possibly multiple biopsies, for sperm retrieval (90). The use of TESE followed by ICSI has resulted in ongoing pregnancies, even for patients with 47,XXY Klinefelter syndrome (91,92). However, the sperm recovery rate with TESE is only about 50% and is even lower with TESA. Further, ICSI after TESE has variable clinical outcomes in patients with testicular azoospermia.

Following ICSI, fertilization and pregnancy rates are significantly lower with

testicular azoospermia than with posttesticular azoospermia (86,93). Moreover, embryos derived from testicular sperm retrieved from men with testicular azoospermia have higher aneuploidy rates and lower developmental competence (94). In comparison with patients who have normal testicular histology, all measures of success are lower in the presence of an associated histologic diagnosis of testicular aplasia, Sertoli cell-only syndrome, or spermatogenesis arrest (92,95,96). Despite these findings, the histologic diagnosis alone should not be used to exclude patients from ICSI treatment because 15% of cases with no sperm identified on histology were found to have sperm on retrieval (97). Among patients with testicular azoospermia, surgically recovered sperm may be at various stages of maturation arrest (i.e., round spermatid, elongated spermatid, and motile and immotile spermatozoa). Although sperm at all stages have been used to establish successful pregnancies using ICSI (53,98), the fertilization and pregnancy rates associated with maturation-arrested spermatid are very low, and couples should be counseled regarding their prognosis and alternative options (99,100,101).

Donor Insemination

For men with azoospermia, couples with significant male factor infertility who do not desire ART, or women without a male partner who are seeking pregnancy, therapeutic donor insemination offers an effective option. A number of important issues surround the use of this form of artificial insemination. First, despite reports that the use of fresh donor semen is associated with higher pregnancy rates than the use of frozen specimens (102), both the Centers for Disease Control and Prevention and the American Society for Reproductive Medicine recommend the use of frozen samples (103). This recommendation stems from the increasing incidence of human immunodeficiency virus (HIV) infection in the general population and the lag time between HIV infection and seroconversion. **Currently, semen donors are screened for HIV infection, hepatitis B, hepatitis C, syphilis, gonorrhea, chlamydia, and cytomegalovirus infections, all of which may be transmitted through semen. All cryopreserved samples are quarantined for 6 months, and the donor is retested for HIV before clinical use of the specimen.** Donors are likewise questioned about any family history of genetically transmitted disorders, including both mendelian (e.g., hemophilia, Tay-Sachs disease, thalassemia, cystic fibrosis, congenital adrenal hyperplasia, Huntington disease) and polygenic-multifactorial conditions (e.g., mental retardation, diabetes, heart malformation, spina bifida). Those with a positive family history of these conditions are eliminated as donor candidates.

A second issue surrounding the use of therapeutic donor insemination—that which is most

important to the patient—is the success rate of treatment. **In patients younger than 30 years of age who have no other infertility factors, conception rates approach 62% after 12 cycles of treatment with frozen sperm (104). In several prospective randomized or crossover trials, IUI was superior to intracervical insemination for donor insemination.** Overall, the cycle fecundity rates ranged from 9.7% to 24% for IUI, to 3.9% to 17.9% for intracervical insemination (105,106,107,108,109,110,111). A meta-analysis concluded that IUI had a significantly higher cycle fecundity rate when compared with ICSI (OR 2.4, 95% CI, 1.5–3.8) (112). Moreover, the concomitant use of *clomiphene citrate* or gonadotropin

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(hMG) for controlled ovarian hyperstimulation (COH) did not result in higher fecundity rates (112). In addition, the length of recommended treatment also should be considered. When frozen donor semen is used, more than 80% of subsequent pregnancies will occur during the first 12 months of treatment (113). Thus, patients who do not conceive within 6 to 12 months should be assessed for female factors and encouraged to terminate treatment or proceed with alternative forms of therapy.

Last, but not least, one must consider the psychosocial aspects of pregnancies involving donor gametes. Among patients without a male partner, the potential repercussions of becoming a single mother and the issue of telling others about the father of the child should be considered. If the couple is married, it is imperative that the husband is aware of the process of using donor gametes. Most programs require that the husband sign a consent form. A skilled infertility social worker or psychologist can be immeasurably helpful in addressing these concerns.

Age and Decreased Ovarian Reserve

An association between the age of the woman and reduced fertility has been well documented. The decline in fecundability begins in the early 30s and accelerates during the late 30s and early 40s. **Chronologic age is the strongest determinant of reproductive success in both spontaneous and ART cycles because it is a predictor of ovarian reserve (114,115). However, age has traditionally not been regarded as a cause of infertility per se, likely because it represents a physiologic rather than a pathologic progression.**

In rural Senegal, where each woman gives birth to an average of 7.9 children, fertility rates peak at 25 years of age and decline steeply after 35 years of age (116). Similarly, among the Hutterites, a communal sect living in the Dakotas and Montana that practiced no contraception and had large families, fertility peaked by 25 years of age, and one third of women were no

longer fertile by 40 years of age (117). In one study, the fecundability of women who underwent donor insemination because of azoospermia in their husbands provided insight into the effects of age on their fertility. It was found that fertility rates began to drop after 30 years of age. The pregnancy rate after 1 year of inseminations was 74% in women aged 30 years and younger, 62% in women aged 30 to 35 years, and 54% in women older than 35 years of age (118).

Oocyte donation programs provide insight into the physiology of declining fertility in older women (Fig. 30.4.). **When embryos produced from oocytes retrieved from younger women were transferred into older women, the pregnancy rates among the older women approximated those of the younger women** (119), **and variations in pregnancy rates were directly dependent on the age of the donors rather than that of the recipients** (119,120,121). In fact, among 260 egg donors (mean age of 30 years) who underwent COH with exogenous gonadotropins, the number of oocytes retrieved per cycle decreased steadily at the rate of 0.24 oocyte per year of increasing age (121). In another study, the use of oocytes from young donors provided cycle fecundity rates of 50% per cycle. The accumulated pregnancy and live birth rates in this investigation reached 95% and 89%, respectively, after up to four cycles of ART (122). **These observations strongly support that it is the age of the oocyte, rather than the age of the endometrium, that accounts for the age-related decline in female fertility.** This oocyte-related decline in fertility is also known as *decreased ovarian reserve*.

Ovarian reserve refers to the size of the nongrowing, or resting, primordial follicle population, which presumably determines the number of growing follicles and the "quality" or reproductive potential of their oocytes. Ovarian reserve is thought to affect how the ovaries respond to pharmacologic doses of exogenous gonadotropins in terms of follicle count, oocytes produced, serum estradiol levels, duration of stimulation, and the quantity of exogenous gonadotropins required. Although age is the best predictor of

ovarian reserve, approximately 10% of women have an accelerated loss of ovarian reserve by their mid-30s, whereas others respond well to COH and achieve pregnancies despite their advanced age. Because of this imperfect correlation between chronological age and ovarian biological age, assays have been developed to assist in the prediction of ovarian responsiveness to COH.

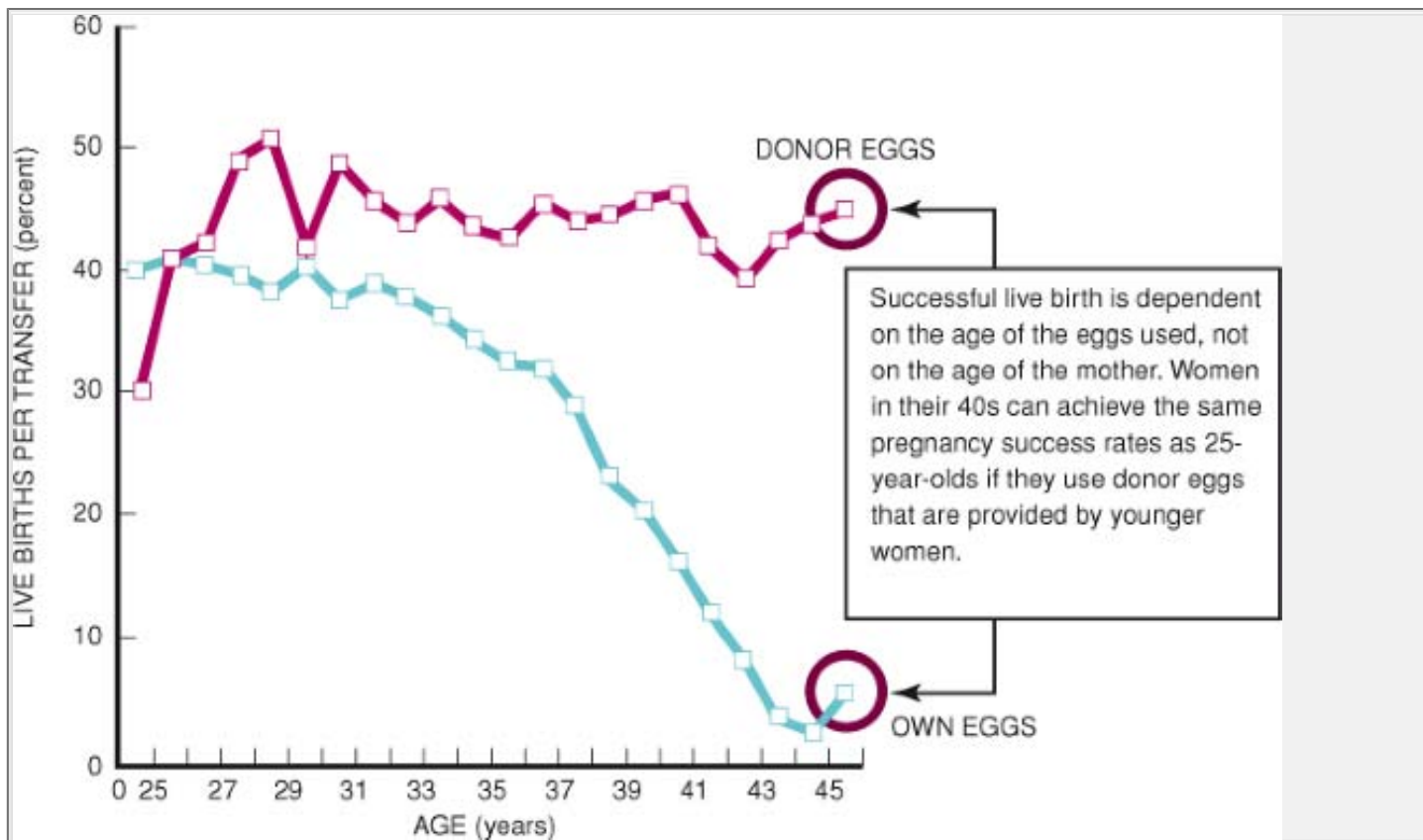


Figure 30.4 Live births per embryo transfer comparing use of a patient's own versus donor oocytes. (From CDC Reproductive Health. 2000 Assisted Reproductive Technology Success Rates. National Summary and Fertility Clinic Reports. <http://www.cdc.gov/nccdphp/drh/art.htm>.)

Screening tests used in the prediction of ovarian responsiveness to COH include assessments of serum day 3 FSH, serum inhibin B, serum mullerian-inhibiting substance (MIS), the *clomiphene citrate* challenge test (CCCT), and transvaginal ultrasound parameters such as antral follicle count and mean ovarian volume measurement (123,124,125). Measurement of day 3 FSH is based on evidence that small increases in basal serum FSH levels correlate with the decreased fecundability seen among women in their late 30s. For IVF treatment following pituitary desensitization, basal FSH assessment proved to be a better predictor of ovarian response than age (126). *Clomiphene citrate* is thought to have antiestrogenic effects on the hypothalamic-pituitary axis, resulting in a decrease in the suppression of FSH production by the pituitary. The CCCT involves the measurement of serum FSH and estradiol on day 3, and again on day 10 after administration of *clomiphene citrate* (100 mg orally each day) from days 5 to 9.

Because FSH levels vary by the assay used and by the population screened, it is recommended that each ART center set its own reference range for evaluating the FSH levels. In a general infertility patient population, the incidence of an abnormal CCCT rises from less than 10% in patients younger than 35 years of age to 26% in patients older than 40 years of age (127). Basal day 3 FSH testing has a sensitivity of 8% in identifying women who will not conceive with subsequent IVF treatment, and the addition of the CCCT to a day 3 FSH only increases the sensitivity of this prediction to 26% (128,129,130). Both day 3 FSH and CCCT results display high specificity (96%) in the prediction of IVF outcome. In one study, 5% of 435 women beginning their first IVF cycle had a day 3 FSH level greater than 15 IU/L (131). These women proved 3.9 times

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more likely to have an unsuccessful treatment cycle. Similarly, among 175 IVF cycles involving women older than 40 years of age, no pregnancies resulted when testing revealed a day 3 FSH greater than 11.1 mIU/mL or a day 10 FSH greater than 13.5 mIU/mL after CCCT (132). Although it is reasonable to advise women with advanced age (greater than 40 years) and abnormal basal day 3 FSH or CCCT results to limit the number of IVF cycle attempts based on their overall poor prognosis, abnormal day 3 FSH and CCCT tests are more difficult to interpret in women younger than 40 years of age with regular menstrual cycles. One retrospective study demonstrated an ongoing pregnancy rate of 47% in women with regular cycles who had FSH levels ranging from 10 to 15 IU/L and 28% in those with FSH levels greater than 15 IU/L (133). These results indicate that high basal FSH values should not be used as the sole basis for excluding women from consideration for ART.

Given the imperfect nature of FSH as a screening test before COH, the search for other assays has intensified. Serum inhibin B is secreted by ovarian granulosa cells starting at the preantral follicle stage (134). **Inhibin B secretion increases during the luteal-follicular transition between menstrual cycles (135), and reflects the overall granulosa cell function of the cohort of follicles that is recruited to undergo gonadotropin-dependent growth. This finding provided the impetus to investigate the potential use of inhibin B as a prognostic marker for ovarian responsiveness in ART cycles.** Inhibin B suppresses the production of FSH by the pituitary gland. In the CCCT, the main mechanism for suppression of FSH is inhibin B production by granulosa cells. Although the use of basal inhibin B levels as a predictor of pregnancy outcomes is debatable (114), several studies have shown the value of stimulated inhibin B in the management of COH cycles. The largest of these studies evaluated the inhibin B level after 4 days of gonadotropin stimulation in 54 patients undergoing IVF (136). Patients with serum inhibin B levels less than 400 pg/mL

had significantly lower numbers of follicles and oocytes. This threshold indicates that stimulated inhibin B yielded a positive predictive value of 86.7% in the prediction of ovarian response to exogenous gonadotropins.

Recently, MIS, also known as antimullerian hormone (AMH), has been investigated as a marker for ovarian reserve and for ovarian responsiveness to stimulation. This substance is produced by the granulosa cells of preantral and small antral follicles and inhibits the initiation of primordial follicle growth (137). The serum level of MIS in women with normal cycles declines with age and becomes undetectable by the time of menopause (138). As the ovarian primordial follicle count decreases, the serum MIS concentration also decreases, making this hormone an ideal candidate for the early detection of ovarian reserve depletion. Decreased levels of MIS in the early follicular phase correlate with poor ovarian response in ART cycles (139). A retrospective study comparing normal and poor responders with gonadotropin stimulation established a threshold value of 8.1 pmol/L, which predicted poor ovarian response during a subsequent IVF cycle with a sensitivity of 80% and a specificity of 85% (140).

The ideal marker for ovarian reserve is one that can be performed in a basal state with high sensitivity and specificity for identifying patients who will have live pregnancy outcomes. Ongoing efforts to identify such a prognostic test are warranted so patients can be counseled regarding various treatment options.

Spontaneous Abortion

Another factor contributing to decreased fecundity among older reproductive-age women is the increased risk of spontaneous abortion in this population. A large study based on the Danish national registry estimated the rates of clinically recognized spontaneous abortion for various age groups to be 13.3% (12–19 years), 11.1% (20–24 years), 11.9% (25–29 years), 15.0% (30–34 years), 24.6% (35–39 years), 51.0% (40–44 years), and 93.4% (greater than 45 years) (141). In addition, using sensitive hCG assays in women during their reproductive years, 22% of all pregnancies were found to be lost before they

could be clinically diagnosed (142). This proportion is thought to be increased among older women attempting pregnancy, making subclinical spontaneous pregnancy loss a significant consideration among older women who are thought to be having difficulty conceiving.

One major cause for the increase in spontaneous losses among older women is

their increased incidence of chromosomally abnormal conceptuses. A cytogenetic analysis of 750 spontaneous abortions revealed that the increase in chromosomally abnormal conceptuses seen with increased maternal age was mainly due to an increase in the incidence of chromosomal trisomies. In particular, the incidence of trisomies 16, 21, 22, 18, and 20 were significantly increased, with 18 and 20 being the most dramatic. In contrast, the risk for monosomy X and polyploidy did not increase with advanced maternal age (143). In conclusion, an increased spontaneous loss rate, coupled with a reduced conception rate, significantly decreases the chance of a live birth among women older than 40 years of age.

Age of Male Partner

There is little doubt that increasing age is accompanied by reduced female fecundity. However, the age-related decline in fecundity for men is more controversial. Male fertility peaks at about 35 years of age and declines sharply after 45 years of age. Yet, men have reportedly fathered children into their 80s (4). Studies using chromosome-specific probes on ejaculated sperm reveal a slight but statistically significant increase in aneuploid sperm with advanced paternal age greater than 55 years (144,145). However, it is not known whether this finding corresponds to an increase in liveborn aneuploidy. Several studies describe an increase in the rate of autosomal recessive disorders among the progeny of men 35 years of age and older (146,147). More recently, advancing paternal age has been associated with an increased incidence of several autosomal dominant diseases, Apert syndrome and achondroplasia, and an increased incidence of schizophrenia (148,149). These findings suggest an age-related decline in gamete quality among men, albeit one that is subtler than that observed in women/E.

Ovulatory Factor

Disorders of ovulation account for about 30% to 40% of all cases of female infertility. These disorders are generally among the most easily diagnosed and most treatable causes of infertility. The normal length of the menstrual cycle in reproductive-age women varies from 25 to 35 days, and most women have cycle lengths of 27 to 31 days. Figure 30.5 shows the fluctuations of estradiol, progesterone, FSH, and LH in a normal, 28-day ovulatory cycle. Women who have regular monthly menses (about every 4 weeks) with minimal symptoms, such as premenstrual breast swelling and dysmenorrhea, almost invariably have ovulatory cycles. Because ovulation is prerequisite to conception, ovulation must be documented as part of the basic assessment of the infertile

...among women with ovulatory factor infertility may include anovulation (complete absence of ovulation) or oligo-ovulation (infrequent ovulation).

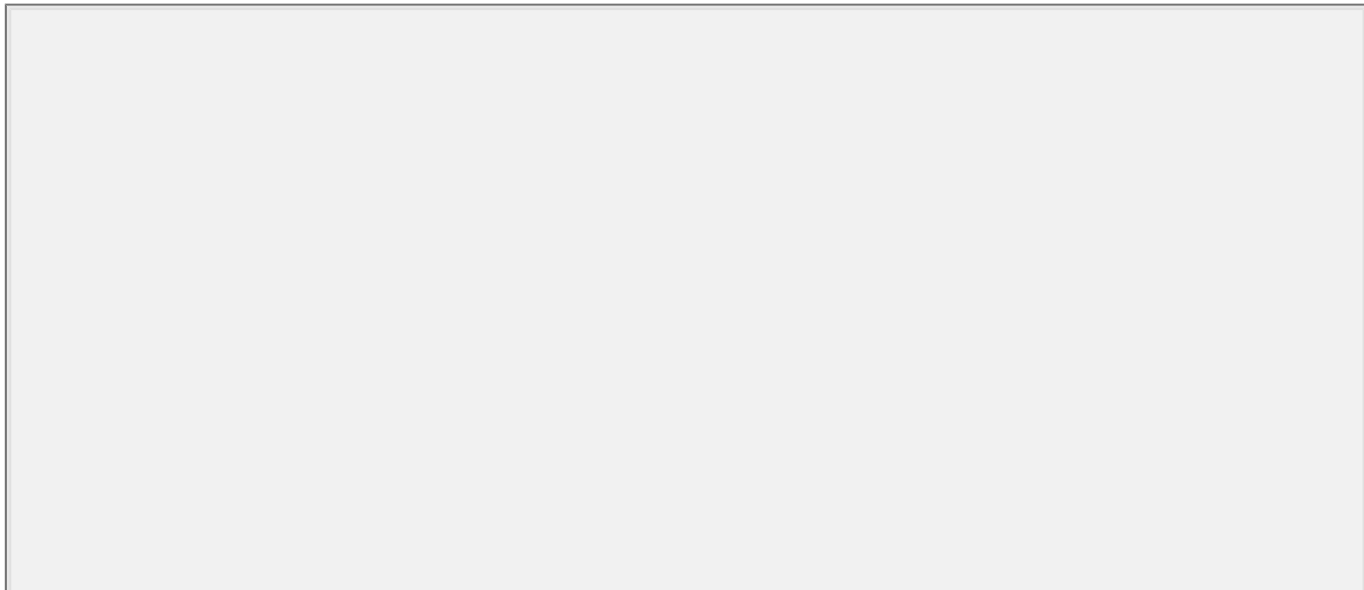
Methods to Document Ovulation

Luteinizing Hormone Monitoring

Documentation of the LH surge represents a remarkably reproducible method of predicting ovulation. Ovulation occurs 34 to 36 hours after the onset of the LH surge and about 10 to 12 hours after the LH peak (150,151). Commercially available kits for documenting the LH surge are generally accurate, quick, convenient, and relatively inexpensive enzyme-linked immunosorbent assays (ELISA) using 40 mIU/mL as the threshold for detection (152,153). The positive and negative predictive values of these kits have been described to be 90% and 96%, respectively

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(154). A 100% correlation between urinary LH prediction of ovulation and transvaginal ultrasound diagnosis of ovulation has further confirmed the value of urine LH detection kits for home ovulation detection (155). Still, this ELISA test cannot detect urinary LH in up to 5% to 10% of women, probably either because of failed recognition by the antibody used or because their peak urinary LH concentration does not rise above the threshold set by the kit manufacturers. Serum LH measurements may be necessary to predict ovulation in such cases.



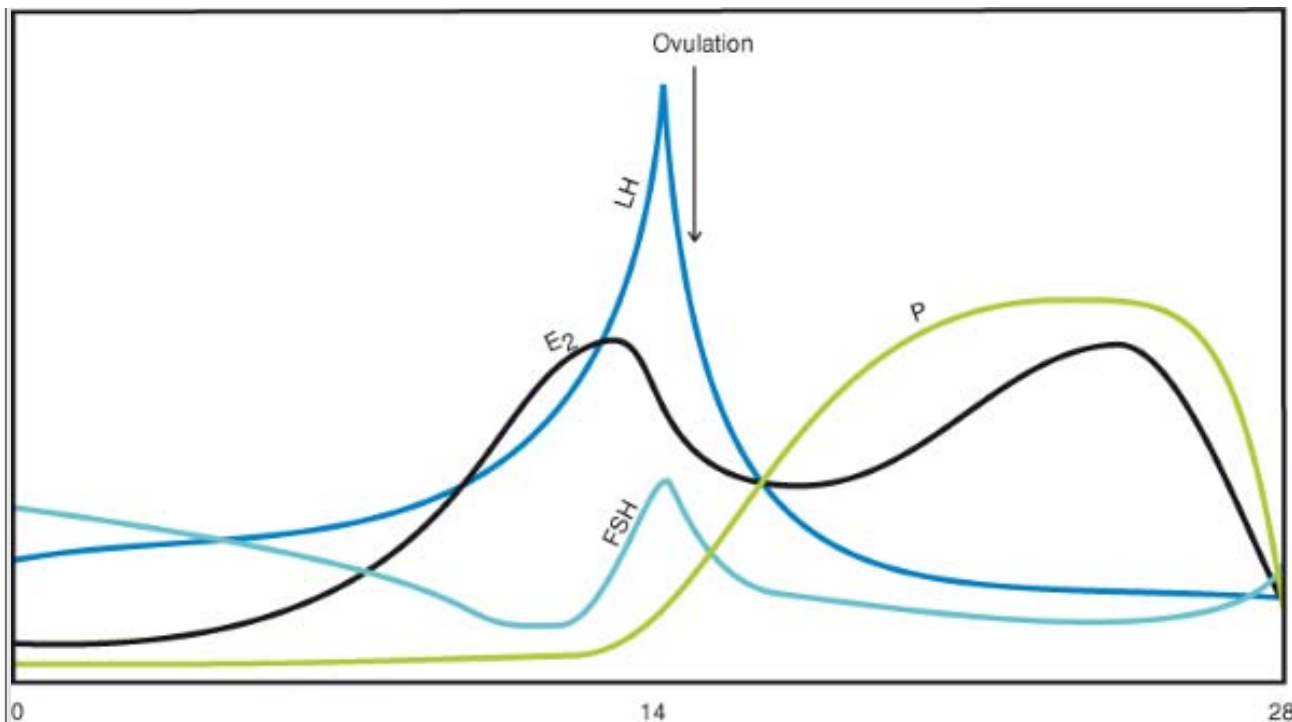


Figure 30.5 Relative hormonal fluctuations in a normal, ovulatory, 28-day menstrual cycle..

Basal Body Temperature

The least expensive method of confirming ovulation is for the patient to record her temperature each morning on a basal body temperature (BBT) chart. The oral or rectal temperature should be determined before the patient arises, eats, or drinks. Smoking is forbidden before temperature measurement, and irregular sleep patterns can interfere with the test results. Patients monitoring their BBT record their temperature daily as well as times when they have coitus. Use of a BBT thermometer is preferred over use of a conventional thermometer because of the instrument's precision in the temperature range under consideration. The principle behind temperature charting as a means to document ovulation is based on the thermogenicity of progesterone. Significant progesterone secretion by the ovary generally occurs only after ovulation. The secretion of progesterone causes a temperature increase of about 0.58°F over the baseline temperature of 97° to 98.8°F typically recorded during the follicular phase of the menstrual cycle. Charting of daily BBTs produces a characteristic biphasic pattern in women with ovulatory cycles. Frequently, a nadir

in charted BBT is noted at the time of the LH surge, but this finding is inconsistent. A normal luteal phase is characterized by a documented temperature elevation lasting at least 10 days.

Charting BBT to document ovulation, although simple, has several drawbacks.

Presumptive ovulation can be identified only retrospectively (i.e., the test merely confirms rather than predicts ovulation). Even retrospectively, the exact time of ovulation is difficult to determine using BBTs, although in most instances, it is probably 1 day before documented temperature elevation. An unequivocal temperature rise generally occurs 2 days after the LH surge and correlates with serum progesterone levels of 0.4 ng/mL (156). In a small percentage of patients, BBT charts are monophasic, despite the documentation of

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ovulation by other methods. Furthermore, BBT charting is correlated with transvaginal ultrasound evidence of ovulation in only 30.4% of cases (155). Despite its limitations, for many patients, BBT charting is a simple way to document ovulation, and unequivocal biphasic cycles are almost certainly ovulatory. Patients with monophasic cycles require confirmation of ovulation using alternative methods.

Midluteal Serum Progesterone

Elevations in serum levels of progesterone constitute indirect evidence of ovulation.

When used to document ovulation, serum progesterone measurement should coincide with peak progesterone secretion in the midluteal phase (typically on days 21–23 of an ideal 28-day cycle). The lower limit of progesterone levels in the luteal phase varies among laboratories, but a level above 3 ng/mL (10 nmol/L) typically confirms ovulation. However, interpretation of isolated luteal-phase measurements of serum progesterone is complicated by the frequent pulses that characterize the secretion of this hormone (157). Although ovulatory levels are often considerably higher than 3 ng/mL, low midluteal serum levels of progesterone are not necessarily diagnostic of anovulation.

Ultrasound Monitoring

Ovulation can also be documented by monitoring the development of a dominant follicle by ultrasound until ovulation takes place. Ovulation is characterized both by a decrease in the size of a monitored ovarian follicle and by the appearance of fluid in the cul-de-sac (158). It most often occurs when follicular size reaches about 21 to 23 mm, although it may occur with follicles as small as 17 mm or as large as 29 mm (159,160). Because of

the inconvenience and expense of serial measurements, routine use of ultrasound for documenting ovulation is discouraged. Instead, its use should be confined to the monitoring of ovulation induction or superovulation.

Follow-up Tests

If test results confirm that a patient is anovulatory or oligo-ovulatory, the differential diagnoses of hypothalamic-pituitary disorder, hypothyroidism, anorexia nervosa, polycystic ovarian syndrome (PCOS), and premature ovarian failure should be considered. In addition to history and physical examination, the basic investigations typically used to assess these potential diagnoses further include serum FSH, prolactin, and thyroid-stimulating hormone (TSH) testing. These three investigations are often sufficient to guide the initial management plan.

Polycystic Ovarian Syndrome

The most common cause of oligo-ovulation and anovulation—both in the general population and among women presenting with infertility—is PCOS. The diagnosis of PCOS is determined by exclusion of other medical conditions *and* the presence of two of the following conditions (161):.

- **Oligo-ovulation or anovulation (manifested as oligomenorrhea or amenorrhea).**
- **Hyperandrogenemia (elevated levels of circulating androgens).**
- **Hyperandrogenism (clinical manifestations of androgen excess).**
- **Polycystic ovaries detected by ultrasonography.**

The exclusion of pregnancy, hypothalamic-pituitary disorders, or other causes of hyperandrogenism (e.g., androgen-secreting tumors or nonclassical congenital adrenal hyperplasia) may be indicated in some patients presenting with presumptive ovulatory disorders and infertility. However, once other causes of oligo-ovulation or anovulation have been

excluded, biochemical evidence consistent with PCOS—including elevated serum LH:FSH ratios and hyperinsulinemia—is not required before initiation of infertility treatment. Before initiating therapeutic changes in such women, differential diagnoses should be reviewed and endocrinologic investigations repeated if necessary. **Because oligomenorrheic women with PCOS are at risk for endometrial hyperplasia, it may**

be prudent to perform an endometrial biopsy before beginning ovulation induction therapy.

Ovulation Induction in Women with Polycystic Ovarian Syndrome

Despite the use of similar medications, the indications and goals of ovulation induction should be distinguished from those of superovulation. **Ovulation induction refers to the therapeutic restoration of the release of one egg per cycle in a woman who either has not been ovulating regularly or has not been ovulating at all.** Although it is usually acceptable for ovulation induction to result in the release of two eggs, one should avoid the ovulation of more than two eggs in an effort to minimize the risk of ovarian hyperstimulation syndrome (OHSS) and multiple gestation. **In contrast, superovulation is indicated for the treatment of unexplained infertility in women who have been unable to conceive despite regular, monthly ovulation. The explicit goal of superovulation is to cause more than one egg to be ovulated, thereby increasing the probability of conception..**

Ovulation induction can be achieved either medically or surgically in women with PCOS. There is no fixed protocol on how to approach ovulation induction in these patients, although it is reasonable to progress from the least to the most invasive therapies. Appropriate patient selection for various therapies can be a significant determinant of the success of ovulation induction among PCOS patients.

Regardless of which treatment is employed, one important concept to convey to couples is that pregnancy is a cumulative probability. Once ovulation has been documented for a particular treatment, patients should be mentally prepared to continue with that regimen for at least three cycles because, for most treatments, the rate of a pregnancy occurring per therapeutic cycle is the same for each of the first three cycles. **When counseling patients, it is often helpful to remind them that even a couple with no fertility problems has a fecundity rate of only 20% to 25% per cycle (1).** A good rule of thumb involves review of

the patient management plan at least once every 2 to 3 cycles and more frequently if side effects are present. This plan should be discussed explicitly with patients, thereby promoting education, communication, and informed compliance.

Weight Loss

A body mass index (BMI) above 27 kg/m² is considered excessive; moreover, an increase in BMI is associated with an increased risk for insulin resistance. There are several excellent reasons for recommending weight loss for infertile patients who are overweight. Weight loss of 20 kg (mean pretreatment weight, 77 kg) through the use of hypocaloric diets in one study and 10 kg (mean pretreatment BMI, 32 kg/m²) in another study resulted in a decrease in plasma testosterone, androstenedione, LH, and fasting insulin levels (162,163). Significant improvement in these parameters, which are thought to play a role in the pathogenesis of PCOS, helps restore spontaneous ovulation in many patients. In a study of 67 overweight women who had a mean weight loss of 10.2 kg/m², spontaneous ovulation and pregnancy occurred in 90% and 30%, respectively (164).

Obese patients are at increased risk for medical conditions such as diabetes, hypertension, and cardiovascular disease. Because obesity also is a risk factor for obstetric complications, there should be tremendous incentive for infertile patients to lose weight (165). As with any other lifestyle change, promotion of weight loss can be difficult and frustrating for both patient and practitioner. Weight loss often requires multidisciplinary efforts, including the involvement of an experienced dietician and promotion of an effective exercise program. However, because weight loss is a gradual process, and other factors may be contributing to infertility concomitantly, it is reasonable to pursue medical options in conjunction with lifestyle changes.

Clomiphene Citrate

Traditionally, *clomiphene citrate* (*Clomid*, *Serophene*) has been the first-line intervention for medical induction of ovulation in PCOS patients.

Clomiphene citrate is a weak synthetic estrogen that mimics the activity of an estrogen antagonist when given at typical pharmacologic doses for the induction of ovulation. A functional hypothalamic-pituitary-ovarian axis is required for appropriate *clomiphene*

citrate activity. More specifically, *clomiphene citrate* is thought to bind and block estrogen receptors in the hypothalamus for prolonged periods, thereby decreasing the normal ovarian–hypothalamic estrogen feedback loop (166). This blockade increases GnRH pulse amplitude in some anovulatory women (167). Increased GnRH levels lead to increased pituitary secretion of gonadotropins, which promotes ovarian follicular development. *Clomiphene citrate* also may affect ovulation through direct action on the pituitary or the ovary (168,169). Unfortunately, the antiestrogenic effects of *clomiphene citrate* at the level of the endometrium or the cervix may have adverse effects on fertility in a minority of individuals (170,171).

Use of *clomiphene citrate* for ovulation induction is generally associated with excellent outcomes. In fact, in some populations, 80% to 85% of treated women will ovulate and 40% will conceive (172,173). Discrepancies between ovulatory rates and conception rates are most likely associated with the number of cycles attempted or are secondary to the presence of additional, nonovulatory infertility factors among treated women. Most pregnancies resulting from induction of ovulation with *clomiphene citrate* occur during the first 6 months of therapy (172). Side effects of *clomiphene citrate* therapy include infrequent OHSS, vasomotor flushes, nausea, pelvic discomfort, and breast pain (174). In the presence of visual abnormalities, *clomiphene citrate* should be discontinued promptly. Use of *clomiphene citrate* is associated with a 35% to 60% incidence of multiple follicular recruitments (175). However, the incidence of multiple gestation with this agent is only about 5% to 8%. Most of these multiple gestations are twin pregnancies, and triplet pregnancies occur infrequently. Rates of spontaneous abortion and teratogenicity in humans are not increased with the use of *clomiphene citrate* (176).

Clomiphene *citrate* is typically used for ovulation induction in the following manner:

- **The drug is supplied in 50–mg tablets; the usual starting dosage is 50 mg/day. A baseline transvaginal ultrasound should be performed on days 1 to 3 to confirm the absence of ovarian cysts before treatment.** Therapy is typically begun within the first 5 days after the onset of a spontaneous or progesterone–induced menses and is continued for 5 days (i.e., treatment on days 2–6, 3–7, or 5–9 of the menstrual cycle) (177). Some patients respond to a dosage as low as 25 mg/day.

- **Ovulation should be documented using a home urine LH kit in conjunction with ultrasound monitoring of follicular development or confirmation by serum progesterone**

at approximately 7 days following the LH surge. This information is valuable for future therapeutic planning because failure to conceive despite successful ovulation has different implications than failure to conceive because of failed ovulation induction. If ovulation does not occur at the initial dosage of *clomiphene citrate*, the dosage is increased in each subsequent cycle by 50 mg/day. The U.S. Food and Drug Administration recommends a maximum dosage of 100 mg/day; however, in patients who ovulate as a result of *clomiphene citrate* treatment, 11.8% do so only at doses of 150 mg/day or more (172). Considerable clinical experience with *clomiphene citrate* indicates that a dosage of up to 250 mg/day is safe.

- **Ovulation is expected to occur 5 to 10 days after the last day of therapy; thus, with standard *clomiphene citrate* regimens, ovulation testing should begin on day 12 or 13 and continue daily until results are positive. Once a pattern is established, ovulation testing can be confined to a better defined 5–day**

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period in subsequent months. Daily intercourse for 3 days beginning on the day of a positive urine LH test may maximize the chance of a pregnancy..

- **Ultrasound monitoring can be used to determine the number and size of follicles that are developing.** If a dominant follicle develops, but there is no spontaneous LH surge, hCG (*Profasi* 10,000 units given intramuscularly, or *Ovidrel* 250 µg given subcutaneously) can be used to induce final follicular maturation and ensure that ovulation is timed optimally with respect to follicular growth and timed intercourse or IUI. The number of *clomiphene citrate*–treated and ovulatory cycles should not exceed six. The maximum cumulative pregnancy rate should be achieved by the six–cycle mark, and further treatment with *clomiphene citrate* is of minimal predicted benefit at that point.

Despite the high therapeutic success rates of *clomiphene citrate* in most anovulatory women, treatment has relatively low success in inducing ovulation in women with PCOS and insulin resistance in whom obesity or elevated BMI also is evident. There is increasing evidence that insulin sensitizers are particularly effective in inducing ovulation in women with PCOS who are insulin resistant..

Insulin Sensitizers

The etiology of PCOS is currently viewed as multifactorial, with contributions from different genetic causes and environmental factors (see Chapter 28) (178). **Insulin resistance is thought to play a central role in the pathogenesis of PCOS in the subset of patients who have increased BMI, hyperinsulinemia, and significant hyperandrogenism** (Table 30.7) (178). **It is also thought that a different form of insulin resistance intrinsic to PCOS is part of the underlying disease mechanism in thin women with PCOS** (179,180).

Therefore, the therapeutic roles of insulin sensitizers, *metformin* and *rosiglitazone*, in ovulation induction have been extensively investigated.

Metformin is an oral biguanide that is approved for the treatment of non-insulin-dependent diabetes. *Metformin* acts by several mechanisms, including inhibition of gluconeogenesis in the liver and an increase in the uptake of glucose in the periphery (181).

When women with PCOS, hyperandrogenism, and hyperinsulinemia are treated with *metformin* for 12 weeks, their fasting insulin and total testosterone levels, free testosterone index, BMI, waist-to-hip ratio, hirsutism, and acne all decrease significantly (182). Moreover, among women who have PCOS, a BMI greater than 28 kg/m², and hyperandrogenemia, 89% ovulate after treatment with a combination of *metformin* and *clomiphene citrate* (182). This rate is significantly higher than the 12% of patients who ovulated with combined *clomiphene citrate* and *placebo* treatment (183). A meta-analysis of studies involving ovulation induction of PCOS patients by *metformin* versus placebo, *metformin* versus *clomiphene citrate*, and *metformin* plus *clomiphene citrate* versus placebo plus *clomiphene citrate* showed that the combined regimen of *metformin* and *clomiphene citrate* increased the success of ovulation induction by three- to fourfold when compared with *clomiphene citrate* alone (184).

Table 30.7 Clinical Findings that Suggest Insulin Resistance and Hyperinsulinemia

Physical findings associated with insulin resistance

Body mass index >27 kg/m²

Waist-to-hip ratio >0.85

Waist >100 cm

Acanthosis nigricans

Numerous achrochordons (skin tags)

From **Barbieri RL**. Induction of ovulation in infertile women with hyperandrogenism and insulin resistance. *Am J Obstet Gynecol* 2000;183:1412-1418, with permission.

Similarly, *rosiglitazone*, an insulin sensitizer belonging to the class of thiazolidinediones, has been shown to induce ovulation within 2 months of treatment in obese, *clomiphene citrate*-resistant patients with PCOS at a rate of 33% when used alone and 77% when combined with *clomiphene citrate* (185). Furthermore, *rosiglitazone* significantly decreases fasting insulin and glucose levels, total testosterone, free testosterone, and dehydroepiandrosterone sulfate (DHEAS) and increases sex hormone-binding globulin (SHBG) (186). Because BMI is not improved by treatment, its ovulation induction effects are presumed to be the result of improved insulin resistance and ovarian androgen profiles (186). The use of *metformin* or *rosiglitazone* alone has been shown to induce ovulation and improve androgen levels in PCOS patients who have normal BMI and insulin sensitivity profiles, although there is no added benefit to combining *metformin* and *rosiglitazone* (187). Thus, the use of insulin sensitizers is not restricted to obese and insulin-resistant PCOS patients. It is anticipated that ongoing investigations in the next few years will further guide patient selection for *clomiphene citrate*, *metformin*, *rosiglitazone*, or combined regimens involving these medications.

Unlike *troglitazone*, which was withdrawn from the market because of its risk of fatal liver failure (1 in 50,000), this newer generation of thiazolidinediones, including *rosiglitazone* and *pioglitazone*, have good safety profiles, especially with respect to liver toxicity (188,189,190). *Metformin* also has an excellent safety profile, but gastrointestinal symptoms are common side effects, and isolated cases of fatal lactic acidosis have been reported in patients with underlying renal compromise. *Metformin* typically is discontinued once pregnancy has been established; however, it is a category B drug, and its administration during pregnancy is not known to confer specific risk to the fetus. Prospective, nonrandomized studies have reported that the continuation of *metformin* in pregnancy appeared safe and may decrease the risk of gestational diabetes (191,192). However, these findings need to be confirmed by a prospective, randomized trial with neonatal and pediatric outcomes before this practice is widely adopted (193).

A typical treatment regimen using *metformin*, with or without *clomiphene citrate*, for ovulation induction in PCOS patients follows (179):.

Select PCOS patients. Failure of ovulation induction with *clomiphene citrate* alone is

an indication but not a requirement for the use of metformin..

- **Confirm normal liver and renal function.** Serum hCG testing to exclude pregnancy, followed by a progestin withdrawal–induced menses, can be undertaken if indicated.

- **Start *metformin* therapy as follows:**

- **Metformin, 500 mg once a day with breakfast for 4 days.**

- **Metformin, 500 mg twice a day with breakfast and dinner for 4 days.**

- **Metformin, 500 mg with breakfast and 1,000 mg with dinner for 4 days.**

- **Thereafter, *metformin*, 1,000 mg twice a day (at breakfast and dinner)..**

- **If a trial of *metformin* alone is chosen, evaluate single serum progesterone levels weekly to detect the occurrence of ovulation.** It may take up to 2 months of therapy for spontaneous ovulation to occur.

- **If *metformin* plus *clomiphene citrate* is the desired regimen, add *clomiphene citrate* at the usual starting dosage of 50 to 100 mg once a day from days 5 to 9 when the full dose of *metformin* has been reached if spontaneous ovulation has not occurred.** Home LH detection kits can then be used to predict ovulation and time intercourse.

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- ***Clomiphene citrate* can be increased incrementally by 50 mg once a day in subsequent cycles if ovulation still does not occur. Once ovulation occurs, the ovulatory dosage of *clomiphene citrate* can be used in combination with *metformin* for as many as 3 to 6 cycles (in conjunction with ovulation detection and timed intercourse or inseminations)..**

If the combination of *metformin* and *clomiphene citrate* fails to induce ovulation, the diagnosis should be reviewed. Alternatively, the aromatase inhibitor *letrozole* has been reported to be efficacious in inducing ovulation in *clomiphene citrate*-resistant patients (194). In patients who have elevated serum DHEAS, *dexamethasone*, 0.5 mg/day at bedtime, combined with typical *clomiphene citrate* regimens may induce ovulation (195). At this low dosage, *dexamethasone* therapy is associated with minimal adverse effects. Other treatment options, including gonadotropin therapy and surgical ovarian diathermy, may be considered.

Gonadotropin Therapy for Polycystic Ovarian Syndrome Patients

Anovulatory PCOS patients who fail to ovulate or conceive after medical treatment with antiestrogen or insulin sensitizing agents should be considered for ovulation induction with gonadotropin therapy, either alone or in combination with *clomiphene citrate* or *letrozole*. This treatment involves daily injection of gonadotropins, close monitoring of serum estradiol levels and monitoring of follicular development by transvaginal ultrasound. Intrauterine insemination often is recommended in conjunction with ovulation induction to optimize the chances of pregnancy. It is important to remember that PCOS patients tend to have a high number of small antral follicles in the unstimulated state. These follicles can potentially be stimulated by exogenous gonadotropin therapy. This effect could be problematic because the goal of gonadotropin therapy in these patients, unlike that in ovulatory patients with unexplained infertility, is not to produce many eggs but rather to induce the release of only 1 to 2 oocytes. Treatment should be monitored by an experienced physician because the risks of OHSS and multiple gestation are significantly increased when using gonadotropins in this patient population.

Surgical Treatment

Pathophysiologic changes in the polycystic ovary have been the subject of many years of intense investigation. As early as 1935, with the initial description of the syndrome, ovarian surgical treatment of PCOS was considered (196). **Initially, surgical management of PCOS involved wedge resection of the ovaries in an effort to reduce the volume of androgen-producing tissue and thereby alleviate hyperandrogenic abnormalities. In fact, ovarian wedge resection does decrease circulating levels of testosterone (197), and this therapy is associated with resumption of menses in 91% of treated**

PCOS patients (198). Unfortunately, many patients treated with ovarian wedge resection suffer from postoperative intrapelvic adhesions, often leading to iatrogenic tubal factor infertility (198,199).

Laparoscopic techniques for treating PCOS appear to be associated with less adhesion formation in the pelvis than noted after ovarian wedge resection by laparotomy (200,201), while maintaining similar improvements in hormonal profiles (202,203). **Compared with controls, patients undergoing laparoscopic ovarian diathermy (or ovarian drilling) have higher rates of subsequent ovulation and a lower resistance to standard ovulation induction agents** (204,205). In further support of this concept, 112 women with PCOS and anovulatory infertility in whom previous ovulation induction attempts using *clomiphene citrate* (up to 200 mg once a day) were unsuccessful were treated with laparoscopic ovarian diathermy. This surgical therapy resulted in a significant decrease in serum levels of LH, testosterone, DHEAS, and androstenedione as well as in the LH:FSH ratio (206). Furthermore, 73% of these patients ovulated spontaneously, 24% ovulated with *clomiphene citrate* therapy, and 1.8% required gonadotropin use alone. The cumulative probabilities of pregnancy were 54%, 68%, and 82% at 12, 18, and 24 months of follow-up, respectively. The median time to conception was 10.2 months. Thus,

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laparoscopic ovarian diathermy may have particular application in ovulation induction among PCOS patients who are resistant to treatment with *clomiphene citrate*.

Laparoscopic ovarian diathermy appears to affect IVF outcomes as well. In a prospective trial comparing IVF outcomes in PCOS patients with and without prior surgical intervention, both a higher ongoing pregnancy rate and lower peak estradiol levels were documented in those who had prior laparoscopic ovarian diathermy (207). If these results are interpreted as an indication that laparoscopic ovarian diathermy favorably alters the response of PCOS patients to COH with gonadotropin therapy, then its effect on reducing the risk for OHSS among PCOS patients treated with these medications warrants further investigation. It is of interest that laparoscopic ovarian diathermy has been linked to a decrease in the elevated rates of spontaneous abortions documented in PCOS patients (206,207).

A variety of techniques have been described for laparoscopic destruction of ovarian tissue in the treatment of PCOS, including the use of laser, unipolar cautery, and bipolar cautery. Although no single technique has been proved superior using randomized studies, recent reports have advocated diathermy by electrocautery (206,207,208). In this technique, the ovary is immobilized, and an insulated

needle is inserted into the ovary in a direction perpendicular to the ovarian surface using a short duration of cutting current at 100 W. Coagulating current at 40 W is then applied for about 2 seconds. The needle is withdrawn, and the process is repeated at up to 15 puncture sites per ovary. At the end of the procedure, the ovaries are lavaged with copious amounts of normal saline (206).

In addition to the usual risks associated with laparoscopic surgery, laparoscopic ovarian diathermy involves the rare but potential risk of surgically induced premature ovarian menopause via inadvertent disruption of ovarian vascular supply. More common, however, is the possible formation of adnexal adhesions, which may further compromise fertility..

Of patients who had second-look laparoscopy after laparoscopic ovarian diathermy, 19% had adhesions (201). In a series of 112 PCOS patients (206), filmy adhesions confined to the ovarian surface were reported in 4 of 15 women who had not conceived at 1 year and who underwent second-look laparoscopy. At present, the impact of postsurgical adhesion formation on subsequent fertility and defined indications for use of second-look laparoscopy in treated patients is undetermined.

Ovulation Induction for Other Anovulatory Disorders

Hyperprolactinemia

Hyperprolactinemia can be associated with ovulatory factor infertility. After exclusion of a pituitary macroadenoma or other intracranial pathology, correction of the hyperprolactinemic state with *bromocriptine* is followed by restoration of ovulation in 90% of patients (209). *Cabergoline* has similarly high efficacy, but it has the advantage of a twice-weekly dosing schedule. More controversial is the use of bromocriptine alone or the addition of *bromocriptine* to *clomiphene citrate* therapy in non-galactorrheic patients with normal or minimally elevated serum prolactin levels. Such therapy has, however, been associated with improved pregnancy rates among normoprolactinemic women with unexplained infertility and galactorrhea (210).

Hypogonadotropic Hypogonadism

Anovulation in the presence of low serum LH, FSH, and estradiol levels defines hypogonadotropic hypogonadism and reflects dysfunction within

the hypothalamic–pituitary axis. Causes of hypogonadotropic hypogonadism, including craniopharyngiomas, pituitary adenomas, arteriovenous malformations, or other central space–occupying lesions, should be excluded using magnetic resonance imaging..

Low BMI is thought to cause anovulation and infertility in women, possibly by disrupting hypothalamic function (211). Examples of conditions characterized by low BMI include anorexia nervosa, rigorous athletic training, and malnutrition. In recent years, the female athlete triad, which consists of secondary amenorrhea, eating disorder or disordered eating, and osteopenia or osteoporosis, has become more widely recognized (212). It is important to understand that the female athlete triad is not restricted to professional athletes, but affects women who train for recreational purposes also. In most patients with this condition, weight gain is the ideal treatment for ovulatory dysfunction, thus avoiding the use of ovarian stimulatory medications and their complications. Other health benefits, including the reduction of pregnancy complications such as intrauterine growth restriction and osteoporosis, can result from correction of an abnormally low BMI. In one study, increased caloric intake and weight gain alone resulted in the resumption of menses in 90% patients with amenorrhea related to low BMI, with 73% conceiving spontaneously (213). In another study, a mean weight gain of 3.6 kg was sufficient to promote the resumption of spontaneous ovulation (214).

There is now increasing evidence linking genetic and physiologic mechanisms to the regulation of body fat content, caloric intake, and hypothalamic control of reproduction. In humans, abnormalities in leptin receptor function lead to early-onset morbid obesity and the absence of pubertal development, presumably secondary to defective hypothalamic function (215). Further, in women with hypothalamic amenorrhea secondary to strenuous exercise or low BMI, daily administration of recombinant human leptin increased LH pulse frequency and mean LH levels within 2 weeks and successfully induced follicular growth or ovulatory cycles within 3 months (216). Leptin, produced by peripheral adipocytes and reflects energy stores, and its receptor have critical functions in body mass regulation, glucose homeostasis, and reproductive function at the level of the hypothalamus (215).

Other conditions of hypothalamic dysfunction, such as congenital hypothalamic failure (*Kallmann syndrome*), can be treated using pulsatile GnRH therapy if the pituitary–ovarian axis is intact. Gonadotropin therapy should be chosen for patients

with pituitary dysfunction, such as those with empty sella syndrome. Each of these treatment modalities is discussed in greater detail under "Gonadotropin Therapy."

Hypothyroidism

The prevalence of abnormal TSH levels in the general infertility population has been reported to be 6.3%, 4.8%, 2.6%, and 1.5% for women in couples diagnosed with anovulatory infertility, unexplained infertility, tubal infertility, and male infertility, respectively (217). This diagnosis is significant in the management of infertility. For instance, one study reported that among 171 women with hypothyroidism, 23% had irregular menses, likely resulting from anovulation (218). Spontaneous ovulatory cycles typically resume when euthyroid status is achieved using *thyroxine* supplementation.

In contrast to the causal relationship between hypothyroidism and anovulation, the association between hypothyroidism or thyroid antibodies and spontaneous abortion is still unclear. Although hypothyroidism has been associated with increased fetal wastage in some studies (219,220), the association between thyroid antibody status and recurrent pregnancy loss or success rates in ART is controversial (221,222,223,224). In any case, because even very mild or subclinical hypothyroidism can have adverse effects on fetal brain development and subsequent intelligence quotient, it is prudent to screen and treat women with thyroid hormone abnormalities before commencing infertility treatment (225).

Tubal, Paratubal, and Peritoneal Factors

Tubal and peritoneal factors account for 30% to 40% of cases of female infertility.

Tubal factors include

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damage or obstruction of the fallopian tubes and usually are associated with previous PID or previous pelvic or tubal surgery. Peritoneal factors include peritubal and periovarian adhesions, which generally result from PID, surgery, or endometriosis. The risk of infertility after a single episode of PID is significant and increases rapidly with subsequent episodes. In fact, the incidence of tubal infertility has been reported to be 12%, 23%, and 54% after one, two, and three episodes of PID, respectively (226). Still, about one half of patients with documented tubal damage have no identifiable risk factors for tubal disease (227). Most of these women are presumed to have had subclinical chlamydial infections.

Hysterosalpingography

The initial diagnostic test used to assess tubal patency, hysterosalpingography (HSG) has a sensitivity of 85% to 100% in identifying tubal occlusion. The specificity of HSG in identifying PID-related tubal occlusion approaches 90% (228,229). Other causes of apparent tubal blockage include salpingitis isthmica nodosa, benign polyps within the tubal lumen, tubal endometriosis, tubal spasm, and intratubal mucous debris (230). Bilateral tubal pathology documented on HSG is associated with significantly reduced fecundity rates and warrants further evaluation using fallopscopy, selective salpingography, or laparoscopy.

HSG usually is performed between cycle days 6 and 11. During menses, HSG should be avoided because there is increased incidence of vascular intravasation caused by dilatation of periuterine veins. Additionally, there is the theoretical risk of retrograde dispensation of menstrual endometrium into the peritoneum with attendant risk of infection and endometriosis. The risk of infectious sequelae after HSG is 0.3% to 1.3%; in high-risk populations, this incidence can be as high as 3% (231,232). Therefore, known hydrosalpinges, current PID or cervicitis, and palpable adnexal masses or tenderness on bimanual examination all constitute contraindications to HSG. **Because there is a high prevalence of current or past chlamydial infection among infertile women and complications of HSG-associated pelvic infection could further compromise fertility, it is reasonable to prescribe antibiotic prophylaxis to patients scheduled for HSG.** A recommended prophylactic regimen consists of *doxycycline*, 100 mg twice daily, beginning the day before HSG and continuing for 3 to 5 days. Other rare complications of HSG include cervical laceration, uterine perforation, hemorrhage, vasovagal reaction, and allergic response to the contrast dye. The procedure often causes uterine cramping; prophylaxis with a nonsteroidal anti-inflammatory medication taken 30 minutes before the procedure may minimize this discomfort.

The performance of the HSG procedure is fairly straightforward. After vaginal cleansing, an acorn (Jarcho) cannula or other injection device is introduced into the uterine cervix. A paracervical anesthetic block is not routinely necessary, but may be used in selected patients. Either a water-soluble or a low-viscosity oil-based (i.e., Ethiodol) dye is used for the procedure. Water-soluble contrast material is more rapidly absorbed than oil-based dyes and does not carry the risk for either lipid embolism caused by dye extravasation or lipid granuloma formation. Conversely, oil-based dyes are associated with less uterine cramping, better resolution of tubal architecture, and a higher postprocedure pregnancy rate (233). In a randomized controlled trial of oil versus water-soluble dye, there was a 33% pregnancy rate with oil and a 17% pregnancy rate with water-soluble dye within nine ovulatory cycles after HSG (234). A meta-analysis found that the use of oil-soluble media to flush the tubes during

HSG significantly increases subsequent pregnancy rates (OR 1.8, 95% CI, 1.29–2.50) (235). Most pregnancies occurred within 7 months of the HSG. A potential mechanism to explain this therapeutic benefit entails flushing of inspissated mucus and debris from the tubal lumen, which allows fertilization to occur. Careful and slow initial injection of 3 to 4 mL of contrast media should give a clear outline of the uterine cavity. Further injection of about 5 to 10 mL of contrast media usually is sufficient to demonstrate bilateral tubal patency or tubal obstruction.

It is not unusual for unilateral tubal fill and spill to occur at the time of HSG. If the tube that fills and spills demonstrates normal architecture and prompt spillage, then it is

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possible that the hydrostatic dye column is following the path of least resistance out of the open tube. Additionally, unilateral or bilateral proximal occlusion may be secondary to procedure-related spastic constriction of the fallopian tubal lumen, which would result in a misdiagnosis of tubal nonpatency. To alleviate the potential for tubal spasm, premedication with diazepam 30 minutes before the procedure has been advocated. If proximal spasm is suspected during the procedure, subcutaneous terbutaline in the amount of 0.25 mg can be administered.

Successful evaluation of proximal tubal obstruction using selective *salpingography* has been described. Based on techniques derived from coronary angioplasty, salpingography uses a small guidewire to permit selective tubal cannulation and radiographic visualization under fluoroscopy.

Other Diagnostic Modalities

Fallopscopy is based on principles similar to selective salpingography but allows direct fiberoptic visualization of tubal ostia and intratubal architecture. **Fallopscopy allows the visual identification of tubal ostial spasm, abnormal tubal mucosal patterns, and even intraluminal debris causing tubal obstruction.** In fact, a tubal disease scoring system based on falloposcopic examination has been suggested to identify patients with poor prognoses for spontaneous conception (236). Complications associated with fallopscopy include a 5.1% rate of pinpoint perforations of the tube.

Alternatively, **sonohysterography with contrast media offers a much less invasive method of diagnosing fallopian tubal obstruction while maintaining a sensitivity and specificity similar to that of laparoscopic chromotubation** (237). Further prospective evaluation and cost analyses are necessary to determine the utility of tubal

cannulation and sonohysterography with contrast media.

Laparoscopy

The most thorough technique for diagnosing tubal and peritoneal disease is laparoscopy. It allows visualization of all pelvic organs and permits detection of intramural and subserosal uterine fibroids, peritubal and periovarian adhesions, and endometriosis. Abnormal findings on HSG can be validated by direct visualization on laparoscopy. Chromopertubation involves the transcervical installation of a dye, such as methylene blue or indigo carmine. Tubal patency is assessed by direct laparoscopic visualization of the dye extruding through the fimbrial openings of the tubes. **Unlike HSG, laparoscopy allows careful assessment of the external architecture of the tubes and, in particular, visualization of the fimbria. Identified abnormalities, including tubal obstruction, pelvic adhesions, and endometriosis, can be treated at the time of diagnosis..**

Treatment of Tubal Factor Infertility

Therapies that directly correct tubal factor infertility are entirely surgical and include (i) correction of periadnexal disease; (ii) correction of proximal, distal, or combined tubal disease; and (iii) correction of iatrogenic tubal abnormalities (e.g., tubal sterilization). **As success rates for ART continue to improve, the indications for surgical approaches in the treatment of tubal factor infertility have become increasingly limited.** Still, many of the principles underlying surgical management remain important. Surgical treatment of periadnexal disease distorting tubo-ovarian relationships has been proved to be effective, regardless of whether the approach is by laparotomy or laparoscopy (238). Adhesion prevention, however, becomes particularly vital when surgery is used to treat prior adhesive disease causing infertility. The relative value of laparotomy versus laparoscopy for the treatment of tubal infertility has received considerable attention, as have their respective effects on postoperative adhesion formation. For example, one study comparing laparoscopy and laparotomy for the treatment of ectopic pregnancy demonstrated that adhesion formation occurred more frequently after laparotomy, even when meticulous technique was maintained during all procedures (239). **Although many adjuncts for**

postoperative adhesion prevention have been proposed, none has consistently deterred postoperative adhesion formation. Thus, the microsurgical principles of

careful hemostatic technique, minimization of tissue trauma, and judicious use of the laparoscopic approach are essential in the surgical management of tubal factor infertility

Proximal Tubal Occlusion

Tubal spasm, temporary mucous plugging, and underfilling of the tube may cause a false-positive finding by HSG when proximal obstruction is demonstrated. The false-positive rate for proximal tubal obstruction may be as high as 15%.

Consequently, confirmation of proximal occlusion by repeat HSG or laparoscopic chromopertubation should be considered. Salpingitis isthmica nodosa, the pathologic sequelae of inflammation in the fallopian tube, accounts for 23% to 60% of histologically confirmed cases of proximal occlusion (240,241). **Proximal tubal occlusion can be corrected at the time of diagnosis by HSG.** Selective salpingography performed under fluoroscopy may be used to inject contrast media directly into the tubal lumen in an attempt to overcome obstruction resulting from mucous plugging. **If selective salpingography fails to recreate tubal patency, proximal tubal cannulation can be performed using a guidewire under radiologic guidance.** Proximal tubal cannulation has a reported success rate of 85% in establishing tubal patency. Reocclusion occurs in 30% of cases. The risk for tubal perforation with cannulation ranges from 3% to 11%, but tubal damage is usually mild and heals spontaneously (230). The ongoing pregnancy rates for selective salpingography and fluoroscopic tubal cannulation in studies averages 26% (230,242,243,244,245,246).

Microsurgical tubocornual anastomosis is the primary surgical approach, with postsurgical ongoing pregnancy rates averaging 47.4% in five reported series involving 175 patients (230,247,248,249,250). Hysteroscopic cannulation appears to have similar efficacy, with a 48.9% ongoing pregnancy rate among 133 patients treated in four series (230,251,252,253,254). **Although ongoing pregnancy rates with microsurgical tubocornual anastomosis and hysteroscopic cannulation appear comparable, cannulation is significantly less invasive and has fewer complications.**

Microsurgery, however, provides access to other pelvic structures, allowing the surgeon to assess the distal fimbriae and to lyse any periadnexal adhesions that may be compromising normal tubo-ovarian relationships. The success of the surgical approach is enhanced by the possibility of subsequent pregnancies without additional treatment. In a study of 102 patients who underwent microsurgical treatment for proximal tubal disease, nearly one half of the women who wanted a second child succeeded over a 2-year period (255).

Distal Tubal Occlusion and Hydrosalpinx

Distal tubal disease and occlusion can be secondary to a variety of inflammatory conditions including infection, endometriosis, or prior abdominal or pelvic surgery. Because of the secretory capacity of cells lining the oviductal lumen, fluid can accumulate within the occluded fallopian tube. The deleterious impact of a hydrosalpinx extends beyond mere blockage of the fallopian tube. The fluid within such a hydrosalpinx may contain substances that are directly embryotoxic or that impede efficient embryo implantation. **A meta-analysis of 14 studies and 1,004 patients with hydrosalpinx concluded that IVF pregnancy rates were significantly lower in cases of hydrosalpinx (256).**

Patients should be selected carefully for surgical correction of distal tubal disease via fimbrioplasty or neosalpingostomy. Fimbrioplasty is the lysis of fimbrial adhesions or the dilation of fimbrial phimosis, whereas salpingostomy (also known as salpingoneostomy) involves the creation of a new tubal opening in an occluded fallopian tube (257). The efficacy of neosalpingostomy or fimbrioplasty as treatment for distal tubal occlusion depends on the extent of tubal and peritubal disease as assessed by HSG and laparoscopy. Poor prognostic factors for successful pregnancy after tubal corrective surgery include hydrosalpinx greater than 30 mm in diameter, thickened tubal walls, absence of visible fimbriae, and dense pelvic or adnexal adhesions (258). The appearance of the tubal

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mucosa has added prognostic significance for the fertility outcome of laparoscopic tuboplasty for distal tubal occlusion (259). Patients with both proximal and distal tubal disease represent the poorest candidates for surgical management of tubal infertility (260). A study of a series of 194 cases of laparoscopic fimbrioplasty and neosalpingostomy resulted in an intrauterine pregnancy rate of 27.3% and an ectopic pregnancy rate of 4.1% (261). Patients younger than 35 years of age with mild distal tubal disease, normal tubal mucosa, and absent or minimal pelvic adhesions may be considered for corrective microsurgery. Otherwise, the extent of disease may render surgery less effective than ART, and the patient should be considered for IVF treatment.

Given the deleterious impact of hydrosalpinges on IVF outcome, the paradoxical situation is presented whereby tubal removal or proximal interruption may actually improve fertility. Removal of a hydrosalpinx that is visualized on transvaginal ultrasound before IVF treatment has been shown to significantly improve outcomes. In a randomized trial of 204 women with ultrasonographic findings consistent with a hydrosalpinx,

the live birth rate was 29% in women who had salpingectomy before IVF and 16% in women who underwent IVF alone (262). A subsequent Cochrane review of three randomized studies confirmed that salpingectomy for hydrosalpinx significantly increases IVF pregnancy rates (263). A technically simpler alternative to salpingectomy is proximal tubal occlusion via cauterization or clip device. **Comparative studies indicate that tubal occlusion is as effective as salpingectomy for improving IVF pregnancy rates in patients with hydrosalpinx** (264).

Sterilization Reversal

About 0.2% of women who choose surgical tubal sterilization request reversal procedures (265,266). The success of tubal reanastomosis depends on the method of sterilization, the site of anastomosis, and the presence of other infertility factors. **Pregnancy rates are lowest (49%) after the reversal of sterilization procedures involving unipolar electrocautery. In contrast, postprocedure pregnancy rates rose to 67% when the sterilization technique involved Fallope rings or spring-loaded clips and 75% when Pomeroy tubal ligation was employed.** The prognosis is best when anastomotic sites have no significant differences in tubal diameter (e.g., isthmic-isthmic or cornual-isthmic anastomoses). Tubal length is also an important prognostic consideration: Final anastomosed tubal lengths of less than 4 cm are associated with low pregnancy rates (267). Pregnancy rates higher than 40% have been reported after microsurgical fimbriectomy correction (268). Laparoscopy to assess surgical prognostic factors, such as potential final tubal length, site of reanastomosis, method of sterilization (if not previously known), and presence of associated pelvic pathology, is often performed before microsurgical fallopian tubal reanastomosis by laparotomy.

Historically, all sterilization reversal procedures have involved laparotomy. More recently, excellent pregnancy rates have been reported after laparoscopic tubal anastomosis. In one study of 186 patients followed after laparoscopic tubal anastomosis with a two-layer closure, cumulative postprocedure pregnancy rates were 60.3%, 79.4%, and 83.3% at 6, 12, and 18 months, respectively (269). In another study, laparoscopic tubal reanastomosis was performed on 102 women, of whom 70% conceived and 65% had ongoing intrauterine pregnancies during the 15-month follow-up period (270). Rates of ectopic pregnancy were similar (3% and 7%) in both series (269,270). The surgical time of laparoscopic tubal reanastomosis depended on the surgeon's experience as well as the number of layers involved in tubal closure.

has been reported. The reported procedures had a mean duration of 159 ± 33.8 minutes and were performed solely using robotic arms that were remotely controlled by surgeons with previous extensive experience with microsurgical tubal anastomosis by laparotomy. The reported postprocedure tubal patency rate was 89% at 6 weeks, and the ongoing pregnancy rate was 50% (271). **Despite advances in surgical technology, however, IVF**

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should be considered for patients with prior sterilization and poor prognostic characteristics. Likewise, IVF is indicated for those patients whose tubal reanastomoses have not yielded a pregnancy by 12 to 18 months postoperatively.

Cervical and Immunologic Factors

Postcoital Test

Cervical factor is estimated to be a cause of infertility in no more than 5% of infertile couples. The classic test for evaluation of the potential role of cervical factor in infertility is the postcoital test (PCT). The PCT is designed to assess the quality of cervical mucus, the presence and number of motile sperm in the female reproductive tract after coitus, and the interaction between cervical mucus and sperm. The test does not yield sufficient information on sperm count, motility, or morphology to allow assessment of semen quality. The PCT should be performed 1 to 2 days before the anticipated time of ovulation because sufficient estrogenization of the cervical mucus is critical to the interpretation of the results. Intercourse after 2 days of abstinence and about 2 to 12 hours before the PCT should be sufficient for testing purposes. Inexpensive and easily performed, the PCT involves both gross assessment of the cervical mucus and microscopic assessment of the sperm–mucus interaction. A small amount of cervical mucus is withdrawn by means of oval forceps or via an angiocatheter syringe. Cervical mucus is assessed for clarity and for spinnbarkeit (i. e., stretchability), with normal estrogen–stimulated mucus stretching 8 to 10 cm when pulled from the cervix. The mucus is placed on a glass slide and covered with a cover slip. A small trail of mucus may be left to dry outside the cover slip so that ferning can be assessed. Estrogenized mucus is clear and watery with a characteristic ferning pattern, whereas progesterone results in mucus that is opaque, thick, and lacking ferning. The presence of sperm, number per high–power field, and motility are assessed by the examination of several microscopic fields. Although the number of motile sperm per high–power field should be documented, normal values have not been established. Some authors suggest that virtually any number of motile sperm seen on the PCT is normal (272), whereas others require greater

than 20 sperm per high-power field (273).

There are several potential causes for an abnormal PCT. The most common is incorrect timing of the test within the menstrual cycle, leading to the production of cervical mucus that is suboptimal for sperm penetration. Other causes of poor mucus quality include anovulation, anatomic factors (e.g., prior cervical conization or cryotherapy), infection, and use of certain medications. *Clomiphene citrate* may exert detrimental effects on cervical mucus by its antiestrogenic action on cervical glands. Poor PCT results may, of course, reflect suboptimal mucus-sperm interactions. The observation of shaking or uniformly dead sperm on PCT may suggest the presence of antisperm antibodies.

Although there is a plausible biologic rationale for the PCT, this test has been accepted without critical review of its prognostic value or of its impact on the overall management plan of the subfertile couple. **The PCT lacks reproducibility, standard methodology, and uniform criteria for assessment. These factors, in conjunction with poor correlation between PCT results and pregnancy outcome, argue against the use of PCT as a standard investigational tool in infertility patients** (273,274,275,276). For example, one study reported no difference in pregnancy outcomes among women whose cervical mucus contained 0 to 11 motile sperm per high-power field (274), whereas another reported abnormal PCTs in 20% of fertile couples (273). A review of the world's English-language literature challenged the validity of the PCT, and found the sensitivity (the ability to detect infertility) of the test to be 9% to 71% and the specificity (the ability to identify fertility) to be 62% to 100% (275). The PCT has no bearing on the management of patients with unexplained infertility because the accepted treatment of superovulation with IUI bypasses

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the cervical mucus. In a prospective, randomized controlled study, couples who underwent PCT as part of their infertility evaluation had cumulative pregnancy rates identical to those of a control group not undergoing PCT after 24 months of therapy (277). **These findings indicate that PCT testing has no effect on treatment outcomes.**

Antisperm Antibodies

Both men and women have the capability to mount a humoral response to sperm. Either allogenic or autoimmune response could, in turn, adversely affect fertility. Antisperm antibodies (ASA) are most commonly limited to immunoglobulin G (IgG), IgM, and IgA isotypes, and each subclass has characteristic anatomic localization. Systemically produced IgG molecules may be found in serum as well as in cervical mucus and semen. Agglutinating antibodies of the IgA class

are typically found in cervical mucus and seminal plasma. The larger IgM antibodies have difficulty traversing the genital tract mucosa and therefore are found exclusively in serum. Antisperm antibodies have also been detected in ovarian follicular fluid (278). In addition to subclassification by isotype, antisperm antibodies can be free, agglutinating, bound to sperm that is motile, or bound to sperm that is immobilized. Further complexity arises in that sperm-bound antisperm antibodies can bind to different parts of the outer sperm plasma membrane, including the head, body, or tail. One major challenge in understanding antisperm antibodies is to determine the relative importance of each of these factors with respect to disease pathogenesis, impact on fertility, and prognosis. Though ASA are present in up to 9% to 12.8% of infertile couples (279), they are also found in up to 2.5% of fertile men (280) and 4% of fertile women (281). These findings would indicate that these antibodies may contribute to subfertility rather than result in absolute infertility.

Many causes have been proposed to explain the formation of antisperm antibodies (271). In women, coital trauma that disrupts the vaginal epithelium could theoretically expose immune effector cells to sperm antigens, thereby leading to antisperm antibody formation. However, it remains unclear why most women, who are repeatedly exposed to millions of spermatozoa, do not exhibit this immune response. In men, the blood-testis barrier normally shields the serum from exposure to sperm and their antigens. Conditions that cause breaks in this barrier could activate autoimmunity. Testicular trauma or torsion, occlusion of the vas deferens secondary to childhood inguinal herniorrhaphy or cystic fibrosis, vasectomy reversal, and genital tract infections have been suggested to elicit antisperm antibody formation.

The mechanisms by which antisperm antibodies might adversely affect fertility remain a subject of debate and ongoing investigation. One or more of these mechanisms could be involved in a particular infertile couple. Adverse antibody-mediated effects on semen quality (either before ejaculation or upon contact of ejaculate with the female reproductive tract) present obvious potential for subfertility. Other purported mechanisms include antisperm antibody-mediated interference with capacitation, acrosome reaction, sperm-egg fusion, and cleavage of the early embryo (282). A recent comprehensive review of the English language literature identified 20 trials examining the effect of ASA on fertilization (32). Of these trials, 14 showed a decrease in fertilization rate, two showed equivocal effect, and four showed no effect.

A number of assays, both indirect and direct, are available for the detection of antisperm antibodies. Sperm agglutination tests (Kibrick's or Franklin-Dukes) and sperm complement-dependent immobilization tests (Isojoma's) have largely been replaced by the immunobead or mixed agglutination tests. The immunobead test uses commercially

available anti-IgG-, anti-IgA-, or anti-IgM-coated polyacrylamide beads. Washed spermatozoa are exposed to the labeled beads, and sperm binding is assessed. The test yields specific information on both the immunoglobulin class of the antisperm antibody and the site of binding to the involved sperm (283). In the mixed agglutination reaction, human red blood cells sensitized with human IgG are mixed with the male's semen. The presence of antibody-coated spermatozoa results in the formation of mixed agglutinates with the red

blood cells (284). A comparison of these two methods demonstrates good correlation of results. However, the mixed agglutination test is easier to perform (279). Though useful in detecting the binding of ASA to various locations on sperm, these tests are not yet capable of determining the antigenic specificities of these antibodies. Until the antigenic specificity is revealed, the exact role of ASA in the impairment of fertilization will remain speculative.

Despite recent improvements in techniques for the identification of antisperm antibodies, the clinical utility of these tests should be limited to very select cases until their prognostic value, impact on infertility management, or effectiveness in treatment can be demonstrated in prospective trials. Corticosteroid therapy for men with antisperm antibodies has been studied in a prospective, double-blind, placebo-controlled trial. This trial did demonstrate decreased antisperm IgG in response to corticosteroid therapy; however, no improvement in sperm-bound IgA or pregnancy outcome was observed (285). In fact, there is currently no support for the use of corticosteroid therapy in antisperm antibody-positive patients because IUI alone has been shown to result in higher pregnancy rates than the combination of corticosteroids and timed intercourse (286). In a couple with no identifiable cause for infertility, a positive or negative antisperm antibody test will not alter their proposed therapeutic plan: superovulation and IUI followed by IVF or ICSI (287). A potential role for ASA testing is in the prospective identification of couples predicted to have high nonfertilization rates with conventional IVF who might benefit from a more expeditious move to ICSI. Yet, a cost-effectiveness analysis using the immunobead ASA assay to screen all patients undergoing IVF revealed a test sensitivity of 11.4% in the prediction of low or absent fertilization as well as a low incidence of test positivity (288). As a result, the cost analysis revealed that screening all patients is collectively more expensive than performing ICSI for couples experiencing an IVF cycle with failed fertilization. Thus, the clinical relevance of ASA testing is currently uncertain.

Uterine Factors

Uterine pathologies are the cause of infertility in as many as 15% of couples seeking treatment (289) and are diagnosed in as many as 50% of infertile patients (290,291,292). For patients undergoing *in vitro* fertilization, lower pregnancy rates are observed in the presence of uterine cavity anomalies (293,294). The correction of these anomalies has been associated with improved pregnancy rates (292). Therefore, the evaluation of the couple with infertility should include an assessment of the endometrial cavity. Most endometrial pathologies implicated in infertility result in both structural and functional impairment. Endometrial molecular mechanisms of implantation and gestation are exquisitely controlled and remarkably complex. Consequently, even subtle defects in endometrial progression from the peri-implantation, luteal phase to the mature decidua supporting a placenta and fetus can result in infertility or early pregnancy loss.

Diagnostic Imaging for Uterine Pathology

Uterine abnormalities that have been implicated in infertility include endometrial polyps, submucous fibroids, intrauterine adhesions, mullerian anomalies, prior exposure to *diethylstilbestrol (DES)*, and possibly luteal phase defect. The diagnosis and treatment of these entities may prove crucial to the successful management of the infertile couple. Insofar as it allows assessment of both tubal and uterine pathology, HSG is a reasonable initial imaging technique to use in the basic infertility evaluation. Although HSG has 85% to 100% sensitivity for detecting tubal pathology (228,229), it is only 44% and 75% sensitive in documenting uterine malformations and intrauterine adhesions, respectively (295).

Sonohysterography appears to be superior to HSG in the detection of uterine malformations, correctly identifying 90% of abnormalities in infertile patients (296). These

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data are consistent with those observed in patients with abnormal uterine bleeding in the general gynecologic setting, where sonohysterography has sensitivities of 87% and 93% in the detection of intrauterine pathology and endometrial polyps, respectively (297,298). Compared with conventional transvaginal ultrasound, sonohysterography has both higher sensitivity (93% versus 65%) and specificity (94% versus 76%) for the detection of endometrial polyps in the patient with abnormal bleeding (298). The use of contrast medium (i. e., Echovist) at the conclusion of saline sonohysterography was initially developed to afford a sonographic assessment of tubal status. When sonographic contrast medium is employed, the study is referred to as hysterosalpingo-contrast sonography, or HyCoSy. A prospective

study investigating the use of HyCoSy as an initial screening study in the infertility evaluation of 103 women demonstrated a 90% concordance between this technique and HSG for the detection of endometrial pathology, but only a 72% concordance in the detection of tubal blockage (299).

Office hysteroscopy has been proven to have superior sensitivity (100%) and specificity (95%) in the evaluation of the endometrial cavity (300). In many practices, diagnostic hysteroscopy is the preferred procedure for the diagnosis of uterine pathology in infertility patients. To optimize visualization of the endometrial cavity during hysteroscopy, the procedure should be performed during the early- to midfollicular phase of the cycle. This also minimizes the possibility of pregnancy. Although excellent acceptance of diagnostic hysteroscopy using a 5-mm scope without analgesia has been reported (301), patient tolerance of office hysteroscopy has been optimized by advancements in pain-control medication regimens. The most important benefit to office hysteroscopy is the ability to immediately treat most pathology that is encountered. Significantly, these operative procedures can be performed using electrolyte distention media. Studies have shown success rates of 98% to 100% with office hysteroscopic procedures (302,303).

Congenital Anomalies of the Uterus

Congenital uterine anomalies may be associated with infertility, spontaneous pregnancy loss in the first or second trimester, or late-trimester pregnancy complications. In women with didelphic, unicornuate, and septate uteri, the rates of spontaneous abortion and preterm delivery are highly increased at 25% to 38% and 25% to 47%, respectively (304). Endometrial dysfunction during the luteal phase may result in infertility, whereas dysfunction occurring after implantation may result in pregnancy loss. Pregnancy outcome in the presence of a uterine anomaly may depend on the location of blastocyst implantation in a particular cycle. This may explain why a woman with a septate uterus might encounter recurrent pregnancy loss after having delivered a term infant. With the exception of a septate uterus, infertility associated with most congenital uterine anomalies is not readily amenable to surgical treatment (305,306). **Laparoscopic-guided hysteroscopic septoplasty can decrease significantly the risk of spontaneous abortion in women with septate uteri, and surgical therapy is indicated in patients with known uterine septi who have recurrent spontaneous abortion** (307). Indications for surgical correction of congenital uterine anomalies when the presenting symptom is infertility are less obvious. Among seven series of hysteroscopic metroplasties performed for infertility, the overall pregnancy rate after treatment was 48% (307). It is still reasonable to consider surgical management in some infertile patients with uterine septi because septoplasty may

maximize the chance of having a live birth by decreasing the associated risks for spontaneous abortion and preterm labor.

In Utero Exposure to Diethylstilbestrol

Exposure to *DES in utero* increases a woman's risk for congenital reproductive tract malformations and obstetric complications, including preterm labor and cervical incompetence (308). In one study, almost 70% of women exposed to *DES in utero* were noted to have uterine malformations on HSG. **The most common malformation was the T-shaped uterus** (309). Whether *DES*-exposed women also have higher rates of infertility remains unclear (310). One investigator reported that decreased fertility in these women was

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particularly prevalent when constriction of the upper segment of the reproductive tract was present (311). This question is difficult to study, however, because there is great variation in the degree of congenital uterine, tubal, and cervical anomalies associated with exposure. Furthermore, some abnormalities may promote other infertility factors. For instance, cervical anomalies may promote production of suboptimal cervical mucus, or cervical stenosis may promote retrograde menstruation and the subsequent development of endometriosis. In fact, a recent large prospective cohort study of patients with laparoscopically confirmed disease identified a significantly elevated risk (RR 1.8, CI, 1.2–2.8) of endometriosis among women exposed to *DES* (312). Overall, when a *DES*-exposed woman has uterine anomalies on HSG and greater than 1 to 2 years of primary infertility, her prognosis for future pregnancy is extremely poor (313). Metroplasty for correction of T-shaped and hypoplastic *DES*-exposed uteri has unproven value and is not recommended. Results of IVF treatment are generally poor in infertile, *DES*-exposed women. **Although ovarian response rates to COH are comparable in *DES*-exposed women and nonexposed women with unexplained infertility, *DES* exposure is associated with significantly lower implantation rates in IVF** (314).

Acquired Abnormalities of the Uterus

Leiomyomas

Among women with infertility and uterine leiomyomas, many variables may affect pregnancy rates, including leiomyoma size, location, and number (solitary versus multiple) as well as

the presence of symptoms associated with these tumors. **Leiomyomas have not been shown to be a direct cause of infertility.** It has been suggested, however, that uterine leiomyomas might alter uterine contractility and thereby disrupt normal sperm migration. Alternatively, the presence of leiomyomas might adversely affect vascular and molecular profiles of sites of implantation (315). **No prospective, randomized trial comparing expectant management with myomectomy in infertile patients with uterine leiomyomas has yet been conducted.** However, one recent case-control study compared pregnancy outcomes among 106 women who had laparoscopic myomectomy for fibroids, 106 women with uterine fibroids who did not have surgery, and 106 women who had unexplained infertility but no fibroids. Reported live birth rates were significantly different among the study populations: 42% for the laparoscopic surgery group, 11% for the group with myomas but no surgery, and 25% for the unexplained infertility group (316). A meta-analysis of 12 prospective series involving a total of 138 women who underwent abdominal myomectomy for infertility showed that cumulative postprocedure pregnancy rates at 1 year were 57% to 67%. Not surprisingly, pregnancy rates for those women who had no other factor contributing to their infertility were higher than for women with additional causes of infertility (61% versus 38%). Women who were treated for submucous fibroids had a postoperative pregnancy rate of 70% at 1 year (317). One study reported 24-month cumulative conception rates of 87%, 66%, and 47% in patients younger than 30 years of age, 30 to 35 years of age, and older than 35 years, respectively, after abdominal myomectomy in 138 infertile women (318). The presence of other causes of infertility and duration of infertility were factors associated with worst prognosis, whereas the size, number, or site of fibroids did not affect pregnancy outcomes. Others have reported success rates after abdominal myomectomy that are comparable to the 65% pregnancy rate and 50% live delivery rate reported for laparoscopic myomectomy (319). The success of laparoscopic myomectomy, however, is contingent on a number of factors, including stringent criteria for patient selection and the surgeon's experience with the procedure. In addition, appropriate closure of the created uterine defect is essential to minimize the complication of uterine rupture during subsequent pregnancy (320,321). **In short, both myomectomy and superovulation/IUI are reasonable treatment options for women with uterine fibroids and otherwise unexplained infertility, particularly if the leiomyomas are large, submucous, solitary, or distorting the uterine cavity.**

Endometrial Polyps

Even in the absence of abnormal uterine bleeding, endometrial polyps may be discovered in women with infertility. The incidence of asymptomatic endometrial polyps in women with infertility has been reported to range from 10% to 32% (303,322). Because of the influence of circulating estrogen on the development of endometrial polyps, the higher incidence seen in the infertility population may be related to the hyperestrogenemia associated with prior cycles of COH. A recent prospective study of 224 infertile women who underwent hysteroscopy suggested a 50% pregnancy rate achieved with polypectomy (323). Timing hysteroscopic evaluation and treatment immediately before COH has proven benefit (292). In contrast, of 83 patients who were diagnosed with an endometrial polyp during COH for IVF and who underwent hysteroscopy immediately after oocyte retrieval, only 58% had histopathologic confirmation of the diagnosis (324). Although pregnancy rates in these women were similar to those of other IVF patients, spontaneous abortion rates appeared higher in those patients with polyps (324). The threshold of parameters, such as size and number of polyps, at which infertility or miscarriage risk is elevated have not been well described. Nonetheless, **the evidence to date indicates that the targeted removal of endometrial polyps to optimize fertility outcomes is prudent..**

Intrauterine Synechiae or Asherman Syndrome

About 13% of 78 infertile women scheduled for IVF treatment were found to have intrauterine adhesions when evaluated with diagnostic hysteroscopy (323). Causes of intrauterine adhesions are often iatrogenic, with patient histories typically involving intraoperative or postoperative complications of uterine evacuations for menorrhagia, pregnancy termination, or postpartum hemorrhage. Other causes of intrauterine synechiae include intrauterine infection with pathogens such as schistosoma and mycobacteria. In some Third World countries, tuberculous endometritis may be an important cause of uterine factor infertility (325). Tuberculous endometritis differs from most other types of endometrial infection, and uterine scarring and infertility are significant sequelae even after treatment (326). Because intrauterine adhesions may interfere with embryo implantation, severe forms of Asherman syndrome have been associated with amenorrhea, menstrual irregularities, spontaneous abortion, and recurrent pregnancy loss.

Hysteroscopic resection is the method of choice for the management of intrauterine synechiae. Postoperative prevention of reformation of adhesive disease may involve estrogen therapy alone or in combination with intraoperative placement of an intrauterine device such as a pediatric Foley catheter for 1 week. It is thought that estrogens will rapidly rebuild the endometrial lining after surgery and thereby prevent the development of

scar tissue. A typical regimen consists of *conjugated estrogen* at a dosage of 2.5 mg to 5 mg per day for 1 to 2 months. **The surgical management of intrauterine adhesions is reported to be very effective, with pregnancy rates higher than 80% among patients treated for mild to moderate disease (327).**

Disorders of Endometrial Function and Luteal-phase Defect

There are few areas of greater controversy in the field of infertility than those surrounding the existence, diagnosis, and treatment of inadequate luteal phase or **luteal-phase defect (LPD)**. The controversy has been fueled by disagreements about both the definition of this entity and the efficacy of its treatment. **Although variously defined, most agree that luteal-phase defect is present when two endometrial biopsies show a delay of more than 2 days beyond the actual cycle day in the histologic development of the endometrium (328).** The actual cycle day has conventionally been calculated by assigning the onset of the menses following biopsy as day 28 and counting backward to the day of biopsy.

Compromising the reliability of endometrial histology in the diagnosis of LPD are the significant inter- and intraobserver variability in the results of histologic dating (329), the intercycle variation of biopsy results, and debate concerning the proper timing of the

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biopsy. In a collection of serial luteal-phase endometrial biopsy specimens from normally fertile women, investigators documented isolated out-of-phase specimens in 31.4% of participants with normal cycles and sequential out-of-phase specimens in 6.6%, suggesting that **out-of-phase endometria are common in women with regular cycles (330).** Others have reported that **the frequency of out-of-phase endometrial specimens among infertile patients is no greater than the rate that would occur by chance alone (331,332).**

In light of the discomfort and inconvenience associated with the multiple endometrial biopsies needed to confirm the diagnosis of luteal-phase defect, investigators have attempted to identify alternative markers for the diagnosis of LPD. In addition to delayed endometrial maturation, LPD can also be characterized by histologic asynchrony between endometrial epithelial and stromal compartments. A variety of factors could be responsible for such histologic alterations, including inadequate follicular development, inadequate FSH or LH secretion, hyperprolactinemia, and inadequate progesterone production by the corpus luteum (333).

Although some studies have advocated the use of a threshold luteal-phase serum progesterone level, data that convincingly associate either single or summed midluteal-phase serum progesterone levels with proposed luteal-phase abnormalities are lacking because of the characteristic pulsatile secretion of progesterone (334). Given the concerns over the accuracy of diagnosing LPD, attempts to diagnose this disorder should be confined to infertile patients who lack other identifiable diagnoses and to those in whom treatment specifically directed at luteal-phase defect is being contemplated.

In recent years, a temporal and functional "implantation window" of maximal uterine receptivity has been proposed to occur during the midluteal phase of the human menstrual cycle. **Studies of IVF and embryo transfer indicate that the implantation window lasts from day 5.5 to day 9.5 postovulation** (335). Using a ratio of urinary estrogen metabolites to progesterone metabolites to time ovulation, the percentage of pregnancy losses associated with implantation on postovulation days 9, 10, 11, and beyond day 11 were 13%, 26%, 52%, and 82%, respectively (336).

Luteal-phase defect has been proposed as a cause of a nonreceptive endometrial environment. Specifically, LPD may result in an aberrant molecular profile within the endometrium, which in turn can adversely affect endometrial receptivity to blastocyst implantation. Given the aforementioned concerns regarding histologic dating, recent studies have been directed toward defining more objective molecular markers of endometrial receptivity. To this end, both the presence of pinopodes and molecular markers, such as the expression of integrins, have been proposed as indicators of uterine receptivity (337,338). Although $\alpha\beta3$ integrin expression and pinopode formation appear to be more reliable markers of the implantation window than histologic dating (339), the clinical utility of testing for their presence is questionable because of the significant intercycle variability and poor reproducibility in their expression (340). The value of $\alpha\beta3$ integrin expression as a predictor of pregnancy outcome has been recently refuted in a cohort of 100 consecutive infertile patients who underwent mid- and late luteal, endometrial biopsy-based histologic dating and immunohistochemistry for $\alpha\beta3$ expression (341).

Current treatments for presumed LPD in infertile patients are empiric and reflect the hypothesis that progesterone insufficiency is causal. Treatment, therefore, involves the administration of vaginal micronized (400–600 mg/day) or intramuscular *progesterone* (50–100 mg/day) beginning 3 days after documentation of an LH surge. After ART with protocols involving a GnRH agonist, supplementation via vaginal administration may be preferred (342).

Progesterone supplementation is typically continued until the first day of the next menstrual cycle

value. If a patient becomes pregnant while on therapy, progesterone is continued until 8 to 10 weeks of gestation. Studies supporting progesterone supplementation for LPD have reported improved pregnancy rates after intervention (343). However, these studies have been small and poorly controlled with varied diagnostic criteria. Therefore, a prospective, randomized trial studying the impact of progesterone supplementation on pregnancy rates and outcomes in infertility patients accurately diagnosed with luteal-phase defect is warranted. Until such a study documents unequivocal clinical relevance, the existence of LPD as an entity will remain controversial.

Infectious Factors

The relationship between subclinical infection and fertility has received considerable attention. Particular interest has focused on two potential pathogens: *Chlamydia trachomatis* and *Mycoplasma* species. The association of chlamydia with PID is well established. Chlamydia is the predominant pathogen detected in about 20% of cases of acute salpingitis in the United States. **Chlamydia may produce asymptomatic infection in the female genital tract, and it is likely that some women experience silent tubal infection.** Despite few if any symptoms, these infections may result in significant tubal damage. A possible link between infection and infertility is suggested by evidence that the prevalence of positive chlamydial cultures may be higher among infertile patients than among controls (344). In a study of 286 women undergoing 344 oocyte retrieval procedures, seropositivity for chlamydia and the presence of bacterial vaginosis were highly associated with tubal disease. Reproductive outcomes of IVF, however, were no different than those of controls (345).

In a study of 771 patients undergoing egg retrieval as part of IVF treatment, the incidence of bacterial vaginosis was 25%. **Although their pregnancy rates were not affected, patients with bacterial vaginosis had a significantly higher risk for spontaneous abortion than matched controls, even after adjusting for smoking history, maternal age, the presence of polycystic ovaries, history of recurrent miscarriage, and history of previous live birth** (346). It remains to be determined which factors directly caused this increased rate of spontaneous pregnancy loss. Likewise, **it is not known whether treatment of bacterial vaginosis before or during IVF treatment would alter the rate of spontaneous abortion.**

Mycoplasma species are pleuropneumonia-like organisms. Both *Mycoplasma hominis* and *Ureaplasma urealyticum* have been recovered from the cervical mucus and semen of infertile couples. There also appear to be higher rates of mycoplasma infection among infertile couples than among fertile couples. The effect of these organisms on fertility is unclear. For example, mycoplasma organisms have been isolated from the cervix of the female partner in 47% of previously infertile couples who conceived and 53% of couples who remained infertile (347). The role of treating these infections in an infertile population also is controversial. In one study, 60% of infertile men who tested positive for ureaplasma and whose infection was subsequently treated by antibiotic treatment impregnated their partners; the rate was only 5% among men whose infection was not treated (348). In contrast, a double-blind study of *doxycycline* treatment for mycoplasma infection failed to show an effect on conception rates (347). **Until a clear association has been established between mycoplasma infection or its treatment and fertility outcomes, routine testing for this organism during an infertility evaluation is not warranted.**

Systemic Illness

In general, any severe systemic illness, such as renal failure, liver failure, or metastatic cancer, can lead to disruption of the hypothalamic-pituitary-ovarian axis and cause infertility.

However, because sporadic ovulation is always possible, even after a period of

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anovulation, use of contraception should be advised if pregnancy is not desired. If a patient with severe systemic illness wishes to conceive, careful preconceptional assessment and counseling is advisable because the risks of fertility treatment and pregnancy can be substantial.

The association of antiphospholipid antibodies, particularly anticardiolipin antibodies and the lupus anticoagulant, with recurrent pregnancy loss led to the investigation of a role for these antibodies in infertility. These antibodies are more prevalent in the infertility population (349). However, the presence of antiphospholipid antibodies has not been found to adversely affect IVF outcomes in a prospective study or in a meta-analysis of seven studies (350,351). **These findings do not support a role for the routine testing of antiphospholipid antibodies in the infertility evaluation.**

Unexplained Infertility

The laboratory assessment of an infertile couple is relatively simple and should

be performed rapidly to establish a diagnosis and initiate appropriate therapy (see Figs. 30.1–30.3). **Evaluation of the man by semen analysis in an accredited laboratory skilled in andrology testing is essential. Ovulation should be documented in women using over-the-counter ovulation detection kits.** If uncertainty surrounding the interpretation of such tests exists, the midluteal serum progesterone level can be assessed to confirm ovulation. Unless laparoscopic surgery is already planned for some other indication, tubal obstruction should be excluded using HSG. If laparoscopy is indicated, laparoscopic chromopertubation can be performed at the time of surgery. Any previous infertility investigations should be reviewed and repeated if the results are in doubt. If the basic evaluation reveals normal semen parameters, evidence of ovulation, patent fallopian tubes, and no other obvious cause of infertility, the couple is diagnosed with unexplained infertility. This diagnosis accounts for up to 30% of couples with infertility (352). **In six randomized studies of couples with unexplained infertility, the cycle fecundity in untreated controls was 3.8%, significantly lower than the 25% fecundity rate observed in normal fertile couples** (353).

Role of Diagnostic Laparoscopy

A controversial issue in the management of unexplained infertility concerns the potential role for laparoscopy in the evaluation of this condition. Previously unsuspected conditions that may be detected during laparoscopy include uterine leiomyomas, peritubal adhesions, and endometriosis. These entities can result in infertility via the distortion of normal tubo-ovarian relationships. Prospective studies have demonstrated HSG to be highly sensitive in the evaluation of tubal patency; thus, laparoscopy is not felt to be necessary to evaluate tubal status when HSG findings are normal. However, **retrospective studies of laparoscopy in infertile patients reveal abnormal findings in 21% to 68% of cases after HSG with normal results** (354). Although the prevalence of pathology exposed by laparoscopy is impressive, the value of the procedure depends on whether it influences treatment decisions or fertility outcomes. In a retrospective review of the laparoscopic surgical reports of 495 couples planned for IUI treatment, laparoscopy revealed abnormalities that changed the treatment decision in 25% of cases (355). The most common disorders encountered in descriptive series include endometriosis (43%) and peritubal adhesive disease (34%) (354).

Whether laparoscopic management of these disorders enhances fertility outcomes remains largely uncertain. In the case of peritubal adhesions, a single nonrandomized study comparing open adhesiolysis versus no treatment showed a

significant increase in the cumulative pregnancy rate at 12 months follow-up (32% versus 11%) (356). Although laparoscopic adhesiolysis has not been studied, it is expected to similarly restore normal tubo-ovarian relationships and optimize fertility outcomes. Validation by a prospective randomized study is warranted.

Endometriosis

The main reason for performing diagnostic laparoscopy in women with unexplained infertility and normal HSG findings is the possibility of identifying and treating endometriosis. The value of diagnosing endometriosis in the absence of tubal obstruction and of its treatment in women with unexplained infertility is an area of considerable debate. It is generally thought that there is a higher prevalence of endometriosis in women with infertility (357). **Clinical evidence linking the presence of endometriosis to infertility exists, but the mechanisms remain unclear. In severe stages of endometriosis, distorted anatomy may explain the association. In cases of minimal or mild disease with normal tubo-ovarian relationships, endometriosis is purported to have a deleterious effect on fertility via associated elevations in a variety of cytokines, including tumor necrosis factor.** These soluble mediators of inflammation may alter the peritoneal, intratubal, or intrauterine environment and adversely affect fertilization, early embryo development, or implantation (358,359,360). Data on the effect of endometriosis on ART pregnancy rates indicate either no significant changes or lower pregnancy rates (361,362,363). The fact that pregnancy rates do not appear to correlate with disease stage (according to the Revised American Society for Reproductive Medicine's classification of endometriosis) further clouds arguments about the importance of endometriosis diagnosis and treatment among infertile couples (364).

Medical therapies for endometriosis that involve hormonal suppression (e.g., combination oral contraceptive pills, GnRH agonists, or danazol) are generally reserved for the treatment of pelvic pain because these treatments preclude pregnancy. Subfertility associated with endometriosis requires alternative, nonsuppressive approaches. In a prospective cohort trial involving 168 infertile women with minimal or mild endometriosis on diagnostic laparoscopy and 263 women with unexplained infertility, the Canadian Collaborative Group on Endometriosis found that fecundity rates were similar in both populations (18.2% versus 23.7%) during 36 weeks of expectant postoperative follow-up (365). The same group performed a randomized

trial comparing 172 women who had ablation or resection of minimal or mild endometriosis with 169 women who were not laparoscopically treated for similar operative diagnoses at diagnostic laparoscopy. Cumulative pregnancy rates were significantly different between treated and control groups at 30.7% and 17.7%, respectively. By 36 weeks of follow-up, fecundity rates were 4.7 and 2.4 per 100 person-months, respectively. The rates of spontaneous abortion (20.6% and 21.6%, respectively) were nearly identical (366). In contrast, the Gruppo Italiano per lo Studio dell'Endometriosi reported that, after 1 year of follow-up, 54 women with otherwise unexplained infertility who underwent resection or ablation of minimal to mild endometriosis had pregnancy rates similar to 47 women whose endometriosis was not treated (24% versus 29%, respectively) (367).

It is possible that any improvement in pregnancy rates resulting from ablation or resection of endometriosis has been so small that a very large trial would be required to document posttreatment differences. It is important to interpret these data in a clinically relevant context. Based on the Canadian prospective randomized trial, it is calculated that one pregnancy would result from the laparoscopic treatment of every 7.7 patients with minimal to mild endometriosis (368). Assuming that 30% of couples with unexplained infertility and otherwise negative findings have mild to minimal endometriosis, 25.4 patients would need to undergo laparoscopy to yield one pregnancy that can be attributed to the treatment of endometriosis (368). In summary, although surgery appears effective for the treatment of endometriosis-associated infertility, the inclusion of a laparoscopic examination in the routine diagnostic evaluation of every infertile patient is subject to debate.

In view of the available evidence, it is reasonable to initiate fertility treatment empirically in women with unexplained infertility and normal HSG findings without assessment of the pelvis by diagnostic laparoscopy. This conclusion is based on a number of issues, including the debated value of diagnostic laparoscopy, known surgical

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risks of laparoscopy, and proven efficacy of empiric treatment. The optimal timing of laparoscopy is undetermined, and diagnostic laparoscopy can be performed if initial treatments are unsuccessful. If laparoscopy is performed, visible endometriotic lesions should either be ablated or resected. A retrospective study has reported electrocoagulation and resection of endometriosis to have an indistinguishable effect on postprocedure pregnancy outcome (369). **The best overall approach to patients with unexplained infertility involves a discussion of the options of empiric therapy or diagnostic laparoscopy and allowing the patient to actively participate in decisions regarding the course of treatment..**

Treatment of Unexplained Infertility

As requirements for both diagnostic laparoscopy and prior exclusion of endometriosis become less stringent in the diagnosis of unexplained infertility, the potential impact of this broader definition on treatment efficacy must be considered. In a retrospective analysis, 131 women with more than 2 years of unexplained infertility were managed expectantly while waiting for IVF. Their pregnancy rate was only 0.9% per exposure cycle, whereas a similar group of 119 women receiving IVF treatment had a 17% pregnancy rate per cycle (370). **The low spontaneous pregnancy rate in these patients warrants the abandonment of expectant management and the rapid initiation of empiric therapies.** These therapies are aimed at increasing the chances of conception by increasing the available numbers and proximity of healthy gametes.

Treatment typically involves superovulation (increasing female gametes); collecting, washing, and concentrating the semen (increasing motile sperm); and bypassing a potential cervical factor using IUI. Superovulation with *clomiphene citrate* and IUI is usually the initial treatment regimen employed. This therapy is fairly efficacious in many couples with unexplained infertility and is less invasive, less expensive, and associated with fewer complications than other forms of treatment. However, if *clomiphene citrate* with IUI is unsuccessful after 3 months of treatment, then COH using gonadotropin therapy should be undertaken in conjunction with IUI (COH/IUI). If both these approaches fail to result in pregnancy, IVF or ICSI can be performed.

Clomiphene Citrate and Intrauterine Insemination

The rationale for using *clomiphene citrate* to increase the fecundity rate in ovulatory women with unexplained infertility is that of superovulation. Use of IUI has become a standard part of the *clomiphene citrate* regimen in treating these women. The degree of superovulation using *clomiphene citrate* is mild and most commonly results in the release of two eggs in ovulatory women. This low degree of superovulation limits complications such as multiple gestation, but it also limits efficacy. In fact, multiple pregnancy occurs in only 10% of patients treated with *clomiphene citrate*, and most of these are twin pregnancies. **A meta-analysis of six randomized controlled trials has shown the use of *clomiphene citrate* in women with unexplained infertility to be superior to placebo in increasing the clinical pregnancy rates per patient (OR 2.37, CI, 1.22–4.62) and per treatment cycle (OR 2.5, CI, 1.35–4.62) (371)..**

In couples with unexplained infertility, IUI significantly improves fertility outcome when performed in *clomiphene citrate*-treated cycles. A literature review of eight studies involving 932 cycles revealed cycle fecundity rates of 5.6% with *clomiphene citrate* alone compared with 8.3% with combined *clomiphene citrate* and IUI (353). Presumably, IUI bypasses the cervical mucus, which may be suboptimal because of the antiestrogenic effects of *clomiphene citrate*. However, *clomiphene citrate* may result in a thin endometrium, for which estradiol administered orally or vaginally improves outcome. In a randomized, double-blind study involving 64 patients with unexplained infertility undergoing superovulation with *clomiphene citrate*, the addition of *ethinyl estradiol* (0.05 mg daily for 5 days starting on day 8) resulted in a thicker endometrium and a higher ongoing pregnancy rate (37.5% versus 6.25%) (372).

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An alternative to *clomiphene citrate* is the aromatase inhibitor, *letrozole*. A prospective randomized trial involving 238 superovulation/IUI cycles in couples with unexplained infertility found that the pregnancy rates are similar for *clomiphene citrate* and *letrozole* (8.9% and 11.5%, respectively) (373). However, the rate of spontaneous miscarriage appeared lower in the *letrozole* group (373). Letrozole is reported to result in a luteal phase endometrium that is in phase and has normal thickness with pinopodes (374). Further, the incidence of a thin endometrial echo on ultrasound (≤ 5 mm) is suggested to be rare in *letrozole* cycles when compared with *clomiphene citrate* cycles (194).

Controlled Ovarian Hyperstimulation and Intrauterine Insemination

IUI is considered a standard adjunct to any superovulation treatment in unexplained infertility. A meta-analysis of prospective, randomized trials comparing IUI and timed intercourse in women with unexplained infertility undergoing treatment with gonadotropins determined that the pregnancy rate is higher with IUI (20% versus 11.4%; OR, 1.84; 95% CI, 1.30–2.62) (375). Given the relative imprecision in the prediction of ovulation, the number and timing of intrauterine inseminations has received considerable study. Traditionally, IUI is timed at 3.6 hours after hCG injection, which is close to the time of ovulation; statistically similar pregnancy rates are achieved when the IUI is timed from 32 to 40 hours after hCG (376). When ovulation detection kits are used, the IUI is performed 24 hours after a spontaneous LH surge. **A meta-analysis of six**

prospective, randomized trials comparing one versus two intrauterine inseminations showed no statistically significant improvement in pregnancy rates with two inseminations (377). However, a subanalysis by mode of ovarian stimulation revealed that when *clomiphene citrate* is used, two IUIs were superior to one (15.2% versus 10.3%; $P = 0.03$) in the optimization of pregnancy rates. In the case of gonadotropin-based ovarian stimulation, two IUIs did not demonstrate statistically significant improvement over a single, well-timed IUI.

In a multicenter, prospective, randomized trial involving 932 couples with unexplained infertility, the combination of COH with gonadotropins and IUI proved superior to IUI alone, intracervical insemination (IC) alone, or COH/IC (49). The National Cooperative Reproductive Medicine Network reported that the pregnancy rate was significantly higher in couples who were treated with COH/IUI (33%) than those treated with IUI alone (18%), COH/IC (19%), or IC alone (10%) (49). However, the multiple pregnancy rates also were increased.

Pregnancy rates using IVF have been reported to be higher than those using COH/IUI in the treatment of unexplained infertility (353,378). **However, the risks and costs associated with IVF treatment are appreciably higher, making it standard practice to treat these couples with COH/IUI before attempting IVF** (353). The question of how many COH/IUI cycles should be attempted before conversion to IVF can be a challenging one, especially because this decision is affected by financial as well as medical factors. The relatively low degree of invasiveness and low costs of COH/IUI must be balanced against the potential decrease in ovarian reserve that can compromise IVF success if treatment is delayed. This is a particularly important consideration for the older, infertile couple. **Therefore, it is good practice to recommend, a priori, a maximum number of COH/IUI cycles that will be attempted.** This definition of treatment expectations may help to temper reactions to unsuccessful therapeutic interventions and foster a sense of control among patients.

It has been recommended that patients with unexplained infertility experience no more than three to six COH/IUI cycles before therapy is discontinued or changed (379,380,381). One study recommended a maximum of three trials of COH/IUI, based on the cycle fecundity and cumulative pregnancy rates observed in historical controls involving 594 patients with unexplained infertility. In this study, the investigators reported a mean fecundity rate per cycle of 16.4% and a cumulative pregnancy rate of 39.2% during the first three COH/IUI cycles. Cycles 4 to 6 yielded a mean fecundity rate per cycle of 5.6%

and a cumulative pregnancy rate of 48.5%, a value only 9.3% higher than the rate achieved with three cycles. Alternatively, a historical control group consisting of 131 patients who failed three cycles of COH/IUI had a cycle fecundity rate of 36.6% in their first attempt of IVF/ICSI treatment (382). **Thus, the benefit of continuing COH/IUI treatment beyond three cycles appears to be minimal for patients with unexplained infertility, unless a move to IVF/ICSI treatment is not feasible for the couple..**

The low rates of pregnancy in patients with unexplained infertility using COH/IUI beyond three cycles might be an indication that two (or more) subsets of populations of patients with unexplained infertility exist. **The fact that a significant proportion of these patients with unexplained infertility will exhibit complete failure of *in vitro* fertilization of oocytes suggests that some of these couples may have major defects in fertilization** (383). The rates of complete failure of fertilization with conventional IVF have been reported to be 11.4% and 17.6% in two studies of couples with unexplained infertility (383,384). The overall pregnancy rate, however, was not increased with the use of ICSI, compared with IVF, in patients with unexplained infertility in a prospective, randomized trial (384). Nonetheless, in this context, IVF might be considered diagnostic in identifying those patients with fertilization defects. Because of their high risk for nonfertilization with conventional IVF protocols, it appears reasonable to offer a split of IVF and ICSI on sibling oocytes within a single cycle for couples with unexplained infertility. This approach would prevent the disappointment and loss of potential pregnancy faced by couples with complete fertilization failure discovered during the first IVF cycle (384).

Treatment Options

Gonadotropin Therapy

Medical preparations of gonadotropins (LH, FSH) can be used to stimulate ovarian follicular development or induce ovulation in the treatment of several conditions: .

- **Ovulation induction in anovulatory PCOS that is resistant to ovulation induction by *metformin* and *clomiphene citrate*.**
- **2. Ovulation induction in hypogonadotropic hypogonadism or pituitary dysfunction.**

Superovulation or COH combined with IUI in the treatment of unexplained infertility.**COH in IVF/ICSI.**

Exogenous gonadotropins supplement or replace the woman's own gonadotropins.

Functional ovarian tissue is required for successful treatment because the major actions of gonadotropins are directed at the ovary itself. Recapitulating spontaneous ovulatory cycles, FSH and LH are presumed to act in concert to stimulate folliculogenesis; FSH acts primarily on the granulosa cells, and LH acts on the thecal lutein cells. When the follicles grow to a certain size, treatment with hCG typically is given to promote oocyte maturation, induce ovulation, and allow appropriate corpus luteum formation and function.

Table 30.8 Different Types of Gonadotropin Preparations					
<i>Trade Name</i>	<i>Name of Compound</i>	<i>Source</i>	<i>Amount of FSH per Ampule</i>	<i>Amount of LH per Ampule</i>	<i>Route of Administration</i>
Repronex (Ferring Pharmaceuticals, Inc.)	Menotropin hMG	Extracted urinary	75 IU	75 IU	IM or SC
Menopur (Ferring Pharmaceuticals, Inc.)	Menotropin urinary hMG	Highly purified	75 IU	75 IU	SC
Bravelle (Ferring Pharmaceuticals, Inc.)	Urofollitropin urinary FSH	Highly purified	75 IU	None	IM or SC
Follistim (Organon Inc.)	Follitropin	Recombinant FSH beta	75 IU ^a	None	SC
Gonal-F (Serono Laboratories, Inc.)	Follitropin	Recombinant FSH alpha	75 IU ^a	None	SC
Luveris (Serono Laboratories, Inc.)	Luteinizing hormone	Recombinant LH	N/A	75 IU	SC

FSH, follicle-stimulating hormone; LH, luteinizing hormone; hMG, human menopausal gonadotropin; IM, intramuscularly; SC, subcutaneously; N/A, not applicable.
^aAlso available in pen formulation.

The key differences in the various preparations lie in the methods of extraction or synthesis of FSH and LH, the proportion of each hormone in the preparation, and the route of administration (Table 30.8). Two prospective, randomized controlled trials that compared hMG and recombinant FSH for ovulation induction in PCOS patients and COH/IUI in patients

with unexplained infertility, respectively, found that the type of gonadotropin used did not affect pregnancy rates. However, the cost was significantly higher when recombinant FSH was used (385,386).

The response to gonadotropins varies from person to person. Even the same individual may respond differently to the same gonadotropin regimen in different cycles. Therefore, one of the advantages of using recombinant FSH is an improved batch-to-batch consistency, allowing a more predictable response to the same gonadotropin dosage. However, since the recombinant forms may not elicit optimal response in patients with particular FSH receptor variants, a trial of hMG or highly purified urinary FSH should be considered in patients who have suboptimal response to recombinant FSH. Finally, patients should undergo a full evaluation to ensure that there are no contraindications to gonadotropin therapy (Table 30.9).

Regardless of the indication, regimens involving gonadotropin therapy for ovulation induction or COH follow fairly similar protocols. All include close monitoring of folliculogenesis using transvaginal ultrasonography and assessment of serum estradiol levels. Such monitoring allows informed adjustment of gonadotropin dosages, timed hCG injection and IUI, and most importantly, limitation of complications such as OHSS and multiple gestation. Patient age, ovarian reserve, and infertility diagnosis should be considered in determining the initial gonadotropin dose, the maximum allowable number of follicles, and the speed of ovarian stimulation (or cycle length). Many protocols have been proposed and have in common the key issues involved in gonadotropin stimulation in non-IVF/ICSI cycles.

Baseline Transvaginal Ultrasound Scan

Patients begin therapy on cycle day 2 or 3 after the onset of a spontaneous or induced menses (cycle day 1 is defined as the first day of menses). A baseline transvaginal ultrasound is performed before gonadotropin injections are begun to identify uterine abnormalities such as endometrial polyps, submucosal fibroids, or congenital defects. Hormonally responsive disorders, including endometrial polyps and submucosal fibroids, may not be apparent at this point in the menstrual cycle, when tissues are in a hypoestrogenic state. Therefore, a systematic survey should be repeated in subsequent ultrasound examinations throughout the course of the stimulation protocol (387). The two-hand transvaginal ultrasound technique often allows better visualization over the one-hand technique. This technique combines current technology with the traditional bimanual pelvic examination. The nondominant hand of the ultrasonographer can be used to apply

pressure to improve the definition of pelvic structures (387). The findings of a thin endometrium (<4 mm) and quiescent ovaries on the baseline scan reflect the hypoestrogenic state of the early follicular phase, which is the optimal state with which to commence treatment. Conversely, a thick endometrium represents endogenous hormonal stimulation above normal basal levels, and further testing should be considered to exclude pregnancy and endometrial hyperplasia.

Table 30.9 Contraindications of Gonadotropins for the Treatment of Infertility in Women

1. Primary ovarian failure with elevated follicle-stimulating hormone levels
2. Uncontrolled thyroid and adrenal dysfunction
3. An organic intracranial lesion such as a pituitary tumor
4. Undiagnosed abnormal uterine bleeding
5. Ovarian cysts or enlargement not caused by polycystic ovary syndrome
6. Prior hypersensitivity to the particular gonadotropin
7. Sex hormone-dependent tumors of the reproductive tract and accessory organs
8. Pregnancy

From **Physicians desk reference**. Micromedex (R) Healthcare Series Vol. 107. Thompson PRD and Micromedex Inc., 1974–2004, with permission.

Unilocular, clear cysts may represent functional cysts or unruptured luteinized cysts. Complex ovarian cysts detected at baseline usually reflect old hemorrhagic corpus luteae and are often seen when the patient has been treated with gonadotropins in the previous cycle. Nevertheless, the differential diagnoses, including endometrioma, benign ovarian tumor, or malignancy, must be considered. The management of ovarian cysts present at baseline is controversial. In 174 prospective, non-IVF, COH cycles, a significantly lower cycle fecundity rate was observed with a baseline ovarian cyst larger than 10 mm (388). Confusion may arise secondary to the findings of several IVF studies that reported no adverse effect on pregnancy outcomes associated with the presence of a baseline ovarian cyst (389,390,391). However, extrapolation of results from IVF studies to non-IVF, COH cycles is not necessarily valid. Regardless, the issue continues to be debated even among IVF studies (392). **Ovarian cysts seen at the baseline scan tend to resolve spontaneously within 1 to 2 months. Low-dose oral contraceptive pills (OCPs) have a lower efficacy**

than older, high-dose OCPs in preventing the formation of new cysts (393,394). Because OCPs do not affect the speed of resolution of old cysts, they are not indicated in this setting..

Starting Dose of Gonadotropin

Gonadotropin dosages can be administered every evening, allowing morning measurements of serum estradiol to reflect the steady state. If the patient has had previous gonadotropin treatment, the starting dose should be based on review of ovarian response in previous cycles. The following guidelines can be used for determining the starting dose of gonadotropins in the first COH or ovulation induction cycle: .

- **With unexplained infertility, the patient's age may affect ovarian response, though it may be difficult to predict.** Other markers of ovarian responsiveness (ie, FSH level, antral follicle count) can assist in tailoring the dose. Though no strict guidelines exist, one should always start at lower doses and increase the dose on days 6 and 7, if necessary. For example, a maximum of 75 to 100 IU of gonadotropin per day should be used for women younger than 30 years of age with a normal FSH level, whereas women older than 40 years of age can be started at a maximum of 150 to 300 IU per day.

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- **Anovulatory PCOS patients should start at 75 IU of gonadotropin per day.** A smaller dose of 50 IU per day sometimes is necessary to minimize the risk for OHSS.
- **Patients with hypogonadotropic hypogonadism usually begin with 75 IU per day.**

Monitoring and Adjustment of Dosage

The dose of gonadotropins is maintained until day 6 or 7, when the serum estradiol level is first measured to document ovarian response. Transvaginal ultrasound also is performed at this time to determine follicular response.

- **If these measurements detect no response, the gonadotropin dosage is increased by 50 to 100 IU per day every 2 to 4 days until a response is evident by rising estradiol levels (or until the maximal dosage is reached).** The maximal dosage is usually 450 IU per day because higher dosages usually do not increase ovarian response (395).

- **Once an ovarian response is obtained, treatment typically is continued without further increase in dose.**

Cycle Progression and Monitoring

Transvaginal ultrasound and serum estradiol measurements are performed every 1 to 2 days to evaluate follicular size, number, and quality. Follicles can be predicted to grow 1 to 2 mm per day after they reach 10 mm, and follicular development is believed to be adequate when maximal follicular diameter exceeds 18 to 19 mm. When hMG is used, the serum estradiol level roughly corresponds to 150 to 250 pg/mL per mature follicle. However, serum estradiol levels may not correlate as closely with the number of mature follicles when recombinant FSH is used. In general, the serum estradiol level can be expected to double every 24 hours if the same dosage of gonadotropins is maintained. Therefore, **the main reasons for monitoring the estradiol levels are as follows:**.

- **To detect missed spontaneous ovulation or premature luteinization, which may be reflected by a drop in serum estradiol levels.**

- **To identify patients at risk for OHSS:**

- **Estradiol levels approaching 800 to 1,000 pg/mL indicate increased risk for OHSS.**

A decrease in gonadotropin dosage should be considered, and 24-hour monitoring is mandated. Withholding gonadotropin in this situation is referred to as "coasting" and is usually followed by a more than 25% decrease in serum estradiol levels while the follicle numbers and diameters increase. If follicle numbers increase to an excessive level, the cycle

should be cancelled (396,397,398).

- **Estradiol levels in the range of 1,500 to 2,000 pg/mL indicate that treatment should absolutely be stopped because of the high risk of OHSS.** All medications should be discontinued, and hCG should not be administered. The patient should be asked to abstain from intercourse until menses occurs because she may spontaneously ovulate. Under these conditions, ovulation and intercourse increase the risk of multiple gestation.

Human Chorionic Gonadotropin Administration

When the largest measured follicle reaches a maximum diameter of 18 to 19 mm or more, 10,000 IU of hCG (*Profasi*) **is administered intramuscularly**. Alternatively, recombinant hCG (*Ovidrel*) can be given at 250 µg subcutaneously (399). Optimal pregnancy rates are achieved with IUI performed at 33 to 39 hours after the hCG injection (376).

Pregnancy Test or Plans for Next Cycle

If menses does not ensue after a treatment cycle, testing for pregnancy should be performed about 15 to 16 days after hCG administration. Testing for serum or urinary levels of β -hCG should not be affected by prior administration of exogenous hCG at this

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point, and β -hCG should be detectable by either method. If pregnancy does not occur, the cycle should be reviewed. If appropriate follicle size, number, and estradiol levels have been reached, there is no need to change the gonadotropin dosage. The dosage should be changed if COH was inadequate or excessive. If the length of the stimulated cycle was too short (ie, the follicular stimulation was too fast), endometrial maturation could have been suboptimal, and the gonadotropin dosage should be decreased in a subsequent cycle.

Special Issues of COH/IUI in PCOS

PCOS patients represent one of the most challenging subpopulations to treat safely and successfully using COH/IUI. The multiple small ovarian antral follicles characteristic of these patients may be very resistant to stimulation, but they are equally likely to respond and grow with minimal increases in gonadotropin dosage. The incidence of multiple pregnancy and

OHSS is increased in these patients (400). Up to 30% or more of COH cycles may be canceled as a result of excessive follicular development. Several approaches that have been proposed to avoid complications of COH and cycle cancellation include downregulation with GnRH agonists, dual suppression with oral contraceptives and GnRH agonists, pretreatment with *metformin*, and surgical ovarian diathermy (206,401,402,403).

Hypogonadotropic Hypogonadism

Therapy with hMG is most successful in patients with hypogonadotropic hypogonadism, yielding cumulative pregnancy rates of 91.2% after six treatment cycles using hMG alone (404). In this particular group of patients, hMG is recommended over purified FSH for ovulation induction because purified FSH has been associated with a significantly higher total dosage requirement, lower estradiol levels, and decreased number of lead follicles (405). Before ovulation induction in these patients, a baseline transvaginal ultrasound should be performed to determine whether the ovaries appear PCO-like, with multiple small antral follicles, thick stroma, or enlarged ovarian volume. A subset of patients with isolated hypogonadotropic hypogonadism have PCO-like ovaries and respond to gonadotropins much like PCOS patients, exhibiting higher serum estradiol levels and a greater number of follicles (406). Based on this finding, in conjunction with the fact that patients with hypogonadotropic hypogonadism typically are younger and have better ovarian reserve than patients with unexplained infertility, it is prudent to start with small doses of hMG in this population to avoid complications of OHSS and multiple gestation.

Hypothalamic Failure

In most patients with acquired hypogonadotropic hypogonadism secondary to cranial surgery or radiotherapy for various cranial tumors, hypothalamic failure is the source of their dysfunctional hypothalamic-pituitary axis (407). In these patients, GnRH stimulation testing and the assessment of endogenous pulsatile LH secretion often can confirm whether the hypothalamic-pituitary axis is intact. Patients with hypothalamic failure and subsequent ovulatory factor infertility represent the best candidates for ovulation induction with GnRH agonists. To mimic physiologic hypothalamic-pituitary interactions, GnRH agonists must be administered in a pulsatile fashion, thereby avoiding the downregulation of the GnRH receptors that accompanies continuous GnRH agonist stimulation. Coexistent growth hormone deficiency or prolactin abnormalities do not affect the efficacy of pulsatile GnRH agonist therapy (407). Because GnRH agonists are degraded rapidly by gastric enzymes (and

either intravenously or subcutaneously with a minipump delivery system. Adverse effects of pulsatile GnRH agonist therapy are mainly related to pump function and route of delivery (i. e., phlebitis at the needle site). The intravenous route is superior (408), but it is recommended that women with a history of bacterial endocarditis be offered only subcutaneous therapy.

In hypothalamic hypogonadotropic hypogonadism, normal negative and positive feedback mechanisms of the pituitary are functional upon treatment with pulsatile GnRH agonists. In this situation, pulsatile GnRH agonist therapy simulates normal physiology and offers some advantages over hMG as a treatment for ovulatory infertility. More

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than two dominant follicles are seen in only 18.9% of patients with hypogonadotropic infertility who are treated with pulsatile GnRH agonist, and more than three follicles are seen in only 5.4% of patients (409). Because OHSS is a rare occurrence, less intensive monitoring is required during GnRH agonist treatment cycles. Moreover, the risk for multiple gestation approximates that associated with *clomiphene citrate* therapy—only 8% (409). These are important advantages when compared with gonadotropin therapies. Cumulative pregnancy rates among women with hypothalamic hypogonadism approach 80% after 6 treatment cycles and 93% after 12 GnRH agonist treatment cycles (410), with no documented increase in the rates of spontaneous abortion (411).

The optimal dosing interval for pulsatile GnRH agonist therapy is 60 to 90 minutes, and the usual recommended dosage is 75 to 100 ng/kg/pulse (405,406). Increased dosage of up to 250 ng/kg/pulse has been reported to be required in the successful treatment of a patient with known GnRH receptor mutation (412). With typical regimens of pulsatile GnRH, ovulation occurs on day 14 and can be documented by standard LH testing. Patients treated with pulsatile GnRH usually benefit from luteal-phase support through continuation of the GnRH pump, administration of hCG, or progesterone supplementation.

Assisted Reproductive Technologies

All methods of ART, by definition, involve interventions to retrieve oocytes. These techniques include IVF, ICSI, gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), cryopreserved embryo transfers, and the use of donor oocytes. Because of improved success rates associated with IVF-embryo transfer, the performance of GIFT and ZIFT has declined in the United States. In 2000, 73,406 cycles of IVF were performed compared with only 549 cycles of GIFT and 763 cycles of ZIFT

(413). Consequently, the following discussion will focus primarily on IVF and ICSI. **The typical ART cycle (IVF or ICSI) has the following main components:.**

- **COH using gonadotropins, follicular development monitoring with transvaginal ultrasound, and assessment of serum estradiol levels.**
- **Prevention of premature LH surge and ovulation.**
- **Oocyte maturation using hCG.**
- **Oocyte retrieval.**
- **Fertilization by IVF or ICSI.**
- ***In vitro* embryo culture.**
- **Luteal support or endometrial preparation using progesterone supplementation.**
- **Transfer of fresh embryos with possible cryopreservation of excess embryos.**
- **First-trimester pregnancy monitoring.**

Folliculogenesis in the Spontaneous Cycle

In unassisted ovulation, the cohort of follicles destined to begin folliculogenesis in any particular menstrual cycle are recruited in the previous cycle's luteal phase. By about the middle of the next follicular phase, one of these follicles will become dominant, and further development of this dominant follicle suppresses maturation of other follicles within the selected cohort of that particular cycle. Follicular-phase growth of a single dominant follicle in unstimulated cycles induces a series of hormonally

regulated feedback loops, resulting in the midcycle LH surge, which is critical for maturation of the oocyte and ovulation. Progesterone production commences just before ovulation and becomes significantly increased after ovulation. Estradiol production during the follicular phase causes proliferation of the endometrial epithelium. Subsequently, progesterone is critical in the final

maturation of the endometrial glands and stroma required for implantation of the blastocyst. **In the presence of successful implantation, the hCG-stimulated corpus luteum serves as the primary source of progesterone until the placenta independently produces sufficient amounts of progesterone by 8 to 10 weeks of gestation..**

Controlled Ovarian Hyperstimulation

Typical use of gonadotropins for COH in ART is similar to the superovulation protocol used in COH/IUI for unexplained infertility. There are several key differences:.

- **When the GnRH agonist luteal downregulation protocol is used, ovarian suppression should be confirmed by a baseline transvaginal ultrasound examination** showing no ovarian cysts larger than 5 cm (389), a thin endometrium, serum estradiol level of less than 50 pg/mL, and serum progesterone level of less than 1.0 ng/mL. Ovarian suppression usually is achieved after about 10 days of GnRH agonist therapy. Once ovarian suppression is confirmed, COH using gonadotropins can be initiated.
- **In ART, the aim of COH is to recruit more follicles than in COH/IUI.** Unlike COH/IUI, the risk for multiple gestation under ART regimens is strictly dependent on the number of embryos that are transferred and not on the number of follicles recruited.
- **The prevention of a premature LH surge and ovulation is critical to the success of ART.** Spontaneous ovulation is prevented by the routine use of a GnRH agonist, or more recently, a GnRH antagonist. Because these regimens help prevent a premature surge, slightly greater flexibility can be exercised on the day of hCG administration without affecting the pregnancy outcomes (414).
-

The removal of granulosa cells during aspiration of each developing follicle with ART is believed to decrease the risk of subsequent OHSS (415). Thus, higher serum estradiol levels and larger follicular sizes are allowed before hCG administration in ART protocols. The risk of OHSS does, however, remain a major concern (416).

Choice of Gonadotropins

In recent years, improved pregnancy rates have resulted from progress in all facets of ART. Concurrent with improvements in embryo culture and embryo transfer techniques has been the introduction of several generations of gonadotropin formulations. The main focus of these improvements has been directed to increasing the purity of the FSH component in new preparations. As a result, current recombinant FSH preparations contain absolutely no LH and no other protein contaminants. A meta-analysis reported that recombinant FSH improved pregnancy rates when compared with use of purified FSH or highly purified FSH (OR 1.20, 95% CI, 1.02–1.42) (417). The effect of recombinant FSH on the incidence of complications in women undergoing ART has been studied. Several randomized, controlled trials have reported a trend toward an elevated incidence of OHSS with the use of recombinant FSH, although this effect has not reached statistical significance (418,419,420). Collectively, these results suggest an important role for recombinant FSH in ART regimens. This conclusion is based on its characteristic batch-to-batch consistency and subcutaneous route of administration, its possible superiority in outcomes over other gonadotropin preparations used in typical COH, its documented benefits over hMG in PCOS patients, and the small increase in ART pregnancy rates as determined by meta-analysis.

Role of Low-Dose Aspirin in ART

By decreasing platelet aggregation and inhibiting vasoconstriction, low-dose *aspirin* is suggested to increase uterine and ovarian perfusion, thereby enhancing outcomes of IVF and ICSI treatments. **A prospective, randomized trial demonstrated that the use of *aspirin* at a dose of 100 mg/day, initiated at the time of GnRH agonist luteal downregulation and continued throughout COH, resulted in**

an improvement in ovarian response, implantation, and pregnancy rates in IVF (421). Consequently, low-dose aspirin has become a standard part of ART protocols in many clinics. However, subsequent prospective randomized studies have

yielded conflicting results regarding the impact of low-dose *aspirin* on pregnancy outcomes in patients undergoing IVF (422,423). Significant complications have not been reported with the use of low-dose *aspirin* in ART..

Recombinant Human Luteinizing Hormone

According to the two-cell theory of ovarian hormone production, stimulation of the theca lutein cells by LH is critical to the overall development of the ovarian follicle. Highly purified FSH contains minimal amounts of LH (less than 0.1%), and GnRH agonist suppresses endogenous pituitary LH and FSH production. Therefore, it has been suggested that supplemental LH might improve folliculogenesis and pregnancy rates when highly purified or recombinant FSH is used for COH in ART. **A prospective, randomized trial comparing highly purified FSH and highly purified FSH combined with supplemental recombinant human LH has reported a trend toward lower implantation and pregnancy rates when recombinant human LH was added to GnRH agonist-downregulated ovulation induction cycles (424).** Although it is possible that some subset of infertility patients might benefit from recombinant human LH supplementation, the generalized use of this hormone in ART currently appears to be limited.

Prevention of Premature Luteinizing Hormone Surge/Ovulation

GnRH-Agonist Downregulation Regimen

The use of GnRH agonist has become standard in ART protocols. It prevents spontaneous ovulation, decreases treatment complications, and allows the control of ovulation to rest exclusively on administration of exogenous medications. Commercial preparations of GnRH agonist consist of decapeptides that differ from the endogenous GnRH agonist at 2 amino acid residues. These modifications increase both the half-life and the receptor binding affinities of GnRH agonist. When used in a nonpulsatile fashion, GnRH agonist causes an initial agonist effect that is accompanied by upregulation of GnRH receptors within the pituitary gland. This initial activity may be manifested as increased gonadotropin effects, which are referred to as the *flare response*. However, continued administration of GnRH agonist downregulates GnRH receptors, resulting in minimal basal production of LH and FSH and no stimulation of the ovarian follicles. Therefore,

GnRH agonists induces a quiescent hypothalamic–pituitary–ovarian axis and a menopauselike state characterized by low estradiol levels. Consequently, in addition to rash or skin irritation at the subcutaneous injection site, it is not uncommon for patients using GnRH agonist to experience side effects such as hot flashes and moodiness.

The most commonly used regimen for superovulation in ART is called the *long, or luteal, downregulation protocol.* In this protocol, GnRH agonist is started in the luteal phase (day 21) of the previous cycle, which minimizes its flare effect and prevents the follicular recruitment that is thought to begin in the luteal phase. The couple undergoing treatment is advised to abstain from intercourse during the cycle before the start of COH; however, concomitant use of GnRH agonist in the presence of an unsuspected pregnancy has not been reported to be associated with increased spontaneous abortion, congenital abnormalities, or pregnancy complications.

Before the adoption of GnRH agonists as a standard part of ART cycles, premature luteinization and spontaneous ovulation presented significant challenges to the success of ART. Prospective, randomized trials indicate that use of GnRH agonist under the long protocol offers many benefits when compared with either no GnRH agonist use or use

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commencing in the follicular phase of the ART cycle (called the *short, or flare, protocol*). Use of GnRH agonist in the long protocol significantly lowered the incidence of premature luteinization and spontaneous ovulation, resulting in a lower rate of canceled cycles (425,426,427). Significantly more oocytes and embryos were yielded using the long protocol, whereas the rate of OHSS decreased (425,427). For logistical reasons, patients preferred the convenience of the long protocol because it requires less frequent monitoring (428). Most importantly, clinical pregnancy rates (425) and live birth rates per retrieval (429) were significantly higher using the long protocol. **The benefits of using the long protocol for administration of GnRH agonists greatly outweigh its disadvantages**, which include daily administration (for most preparations, e.g., leuprolide acetate), increased requirement for gonadotropins, and an overall increase in the cost of medication. In a meta-analysis reviewing the efficacy of various GnRH agonist regimens, the authors concluded that the addition of GnRH agonist downregulation to ovulation induction regimens for ART was advantageous (430). They noted an improvement in pregnancy rates and a decrease in cancellation rates with no associated increase in spontaneous abortion rates.

The debate concerning the choice of long or short GnRH agonist protocols was mostly settled by a large, prospective, observational, multicenter study involving 1,244 couples receiving their first

IVF or GIFT treatment. Although serum estradiol levels were higher in patients using short protocols, these patients had 11% fewer oocytes retrieved. Further, the clinical pregnancy rate was 35% lower using the short protocol when compared with the long protocol, even after adjusting for factors such as age, infertility diagnosis, IVF or GIFT therapy, and year of treatment (431). **Currently, the long GnRH agonist protocol is generally recommended for most patients, and use of the short protocol in ART patients with poor ovarian response has not been proved beneficial** (431).

Many other regimens have been suggested for the administration of GnRH agonists in gonadotropin-stimulated cycles. Some of the more commonly used protocols and gonadotropins are summarized in Fig. 30.6. and Table 30.8.

GnRH–Antagonist Regimen

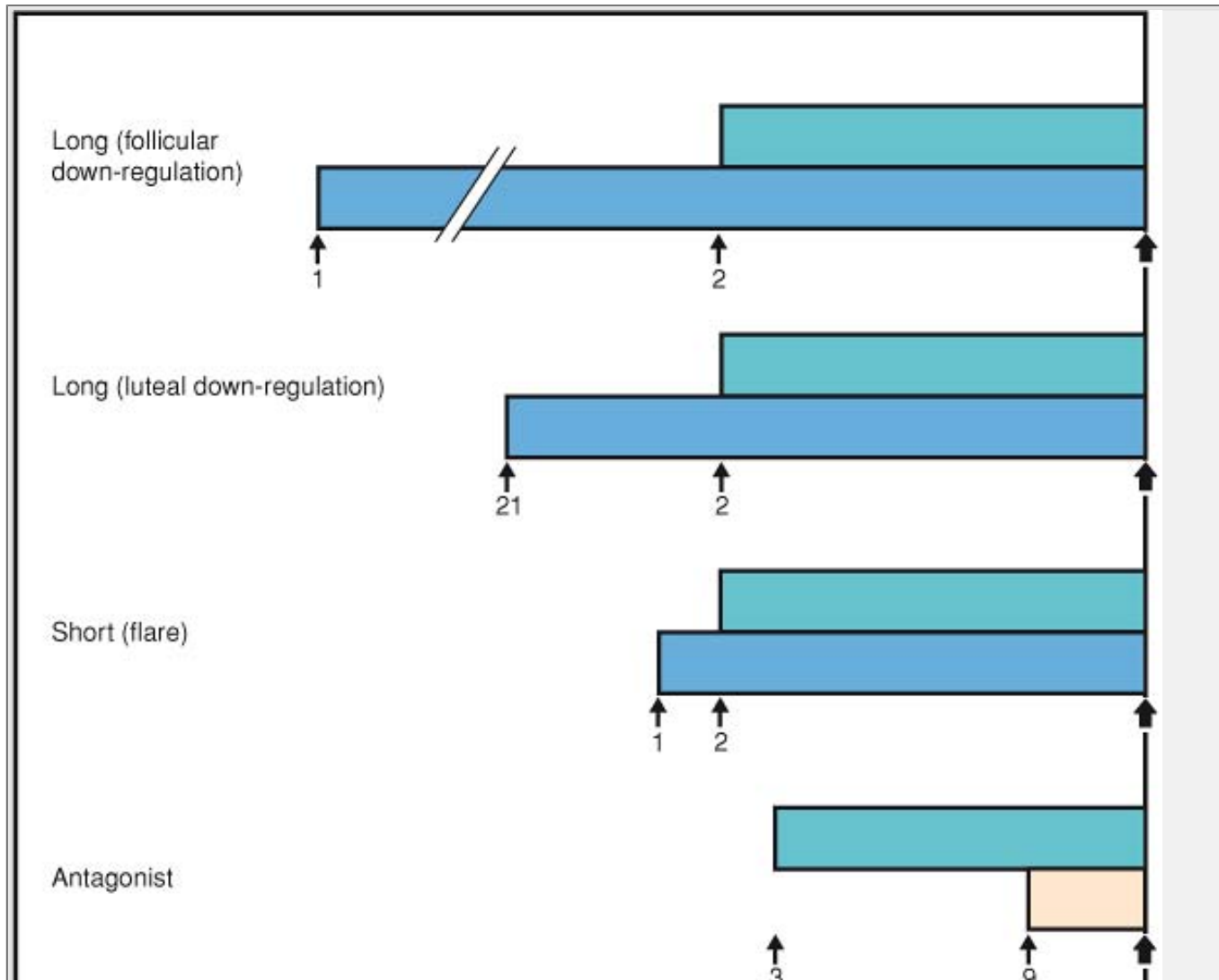
New GnRH antagonists (*Cetrorelix* and *Ganirelix*) have been developed and approved for use in ART protocols. These agents compete with natural GnRH for binding to membrane receptors on pituitary cells and thus control the release of LH and FSH in a dose-dependent manner. The onset of LH suppression is approximately 1 to 2 hours post-administration depending on the dosage used. This suppression is maintained by continuous treatment, and there is a more pronounced effect on LH than on FSH. An initial release of endogenous gonadotropins has not been detected with the use of GnRH antagonists. Because they avoid the flare effect associated with the use of GnRH agonists, they can be started concurrently with gonadotropins and do not require additional time for downregulation. Typically, the antagonist is administered by daily subcutaneous injection, beginning on cycle day 7 or, more commonly, when the lead follicle reaches 14 mm in diameter (432). Alternatively, the medication may be administered as a single bolus dose on approximately cycle day 8. **A Cochrane review of five randomized controlled trials comparing GnRH agonist (long protocol) versus antagonist use in ART cycles showed equivalent efficacy of the two protocols in the prevention of premature ovulation** (433). However, there were significantly fewer pregnancies with the GnRH antagonist protocol (OR 0.79, 95% CI, 0.63–0.99). A significant reduction in the incidence of severe OHSS was observed in the antagonist regimen compared with the long GnRH-agonist protocol (RR 0.36, 95% CI, 0.16–0.80).

hCG Injection

The injection of hCG induces oocyte maturation before retrieval. The dosage of hCG typically is 10,000 IU given intramuscularly or subcutaneously, or 250 µg recombinant hCG

given subcutaneously. Different criteria for hCG injection during COH for ART have been described, but all usually include the presence of one or

two leading follicles with mean diameters larger than 16 to 18 mm, at least two other follicles with mean diameters larger than 14 mm, and serum estradiol levels above defined threshold levels of 300 to 500 pg/mL. Each IVF center sets site-specific criteria based on its own experience and pregnancy outcomes. The overall goal, however, is to time the hCG injection in such a way that the probability of pregnancy is maximized while the probability of premature ovulation is minimized.



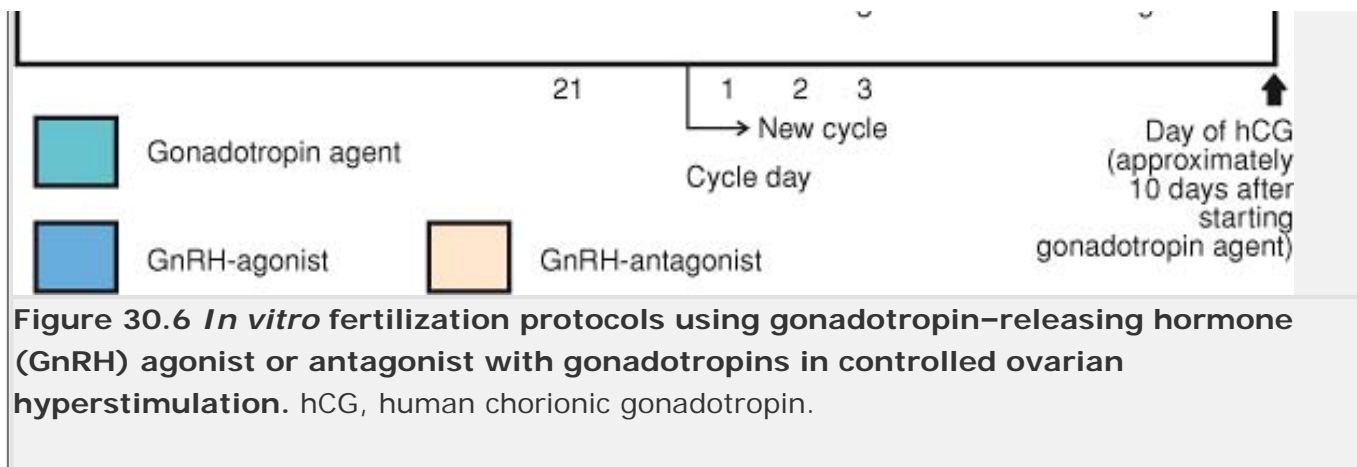


Figure 30.6 *In vitro* fertilization protocols using gonadotropin–releasing hormone (GnRH) agonist or antagonist with gonadotropins in controlled ovarian hyperstimulation. hCG, human chorionic gonadotropin.

Oocyte Retrieval

Oocyte retrieval typically is performed 35 hours after the hCG injection.

Although historically performed by laparoscopy, laparoscopic oocyte retrieval has now been replaced by the transvaginal ultrasound–guided approach.

Transvaginal ultrasound–guided retrieval is markedly less invasive than its laparoscopic counterpart, and the use of ultrasound permits the surgeon to visualize the location of the needle within each ovarian follicle. Intravenous sedation is commonly used for transvaginal ultrasound–guided oocyte retrieval (434,435).

Because the vaginal canal and wall are traversed while using transvaginal ultrasound–guided oocyte aspiration, the possibility of iatrogenically infecting the patient or her oocytes deserves particular consideration. Sterile normal saline usually is used for surgical preparation during

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(oocyte retrieval. In one prospective, randomized trial comparing sterile normal saline to 1% *povidone–iodine* for this application, the former had higher associated pregnancy rates while maintaining low infection rates (436). Although the exact mechanism for this finding is unclear, it is hypothesized that contact with *povidone–iodine* could potentially harm oocytes. Therefore, **if *povidone–iodine* is used, it is recommended that the vagina be lavaged with normal saline after preparation. In addition, routine antibiotic prophylaxis is recommended for transvaginal ultrasound procedures. Such prophylaxis reduces the incidence of postprocedure positive microbiology cultures of embryo catheter tips in 78% of patients undergoing embryo transfer. The importance**

of this effect is suggested by the fact that lower implantation and pregnancy rates are associated with positive microbial catheter–tip cultures (437)..

Performance of the retrieval uses a long, 16– or 17–gauge needle, secured by a guide onto the transvaginal ultrasound probe. The needle is used to traverse the upper vaginal wall and enter into a follicle under direct, real–time transvaginal ultrasound guidance. Follicular fluid is then aspirated into sterile, prewarmed culture tubes. This process is repeated until all the follicles are aspirated. At the end of the procedure, a speculum is inserted into the vagina, and the cervix and vaginal walls are inspected for bleeding. **Although transvaginal ultrasound–guided oocyte retrieval is both rapid and minimally invasive, all potential risks, albeit rare, should be clearly explained to the patient before IVF treatment begins. These risks include the following:**

- **Excessive bleeding, possibly requiring blood transfusion.**
- **Potential needle–induced injury to structures in proximity to the ovaries, including bowel, bladder, and major blood vessels, which may require repair by emergency laparotomy, resulting in an abdominal surgical scar.**
- **Late infectious complications, such as abscesses in the peritoneum, bowel, ovary, or uterus, which may require hospitalization for intravenous administration of antibiotics or surgical interventions. (In the specific case of iatrogenic tubo–ovarian abscess, failure of medical treatment may necessitate surgical removal of the tubes and ovaries.)**
- **Risks associated with intravenous sedation or general anesthesia.**
- **A remote risk that no oocytes will be obtained or fertilized.**

IVF and ICSI

Fertilization of the human oocyte by human sperm *in vivo* requires the interaction

of capacitated spermatozoa with ovulated oocytes, most often within the ampullary portion of the fallopian tube. Capacitation of sperm takes place in the female reproductive tract and involves both changes in sperm motility and changes in the sperm cell membrane that allow the acrosome reaction. Acrosome-reacted sperm are able to penetrate the oocyte's cumulus oophorus and zona pellucida, binding to the oocyte cell membrane and promoting fertilization. The interaction of spermatozoa and oocyte is not a chance occurrence; complex oocyte-sperm intercommunications appear to play an important role in this process (438).

The mandate of the ART team is to attempt to recreate precisely those processes known to occur in unassisted conception. In all ART procedures, male gametes are initially collected directly by ejaculation into a sterile cup. They are then processed, concentrated, and incubated in protein-supplemented media for 3 to 4 hours before being used for fertilization. This final incubation allows for sperm capacitation. Before fertilization, retrieved oocytes also are cultured in protein-supplemented media for about 6 to 8 hours. For IVF purposes, 50,000 to 100,000 capacitated sperm are placed in culture with a single oocyte; 16 to 20 hours later, fertilization is documented by the presence of two pronuclei within the developing embryo.

Indications for ICSI are discussed under the section of "Male Factor Infertility." The procedure itself begins by stripping all granulosa cells from the aspirated cumulus complex

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(oocyte and surrounding cells). This is followed by micromanipulation of egg and sperm under magnification. A holding pipette is used to stabilize the egg while an injection pipette is used to insert a viable sperm into the ooplasm of the egg.

Luteal Support

The act of retrieving oocytes and associated granulosa cells may adversely affect subsequent corpus luteal function, resulting in subsequent progesterone insufficiency. Therefore, the requirement for luteal support represents yet another way in which ART cycles differ from COH/IUI protocols. **Luteal support is usually initiated on the day after oocyte retrieval for ART. Commonly used regimens include the following:**

- ***Progesterone in oil 50 mg, once a day, intramuscularly.***

- **Vaginal progesterone suppositories, 200 mg twice to three times a day.**

- **Oral micronized progesterone, 200 mg twice a day.**

Despite similar levels of circulating progesterone, the oral regimen is associated with decreased per-embryo implantation rates when compared with use of intramuscular progesterone (439).

Embryo Transfer

In unassisted conception, the fertilized oocyte traverses through the fallopian tube for 2 to 3 days before entry into the uterus for implantation. This transport is largely dependent on directional ciliary movement within the fallopian tube, although tubal muscular contractions may be involved (440). The embryo is normally at the morular or early blastocyst stage of development when it reaches the uterine cavity. By this time, and under the influence of luteal-phase levels of progesterone, the endometrium has undergone the decidual changes that prepare it for implantation. **The embryo resides in the intrauterine cavity for 2 to 3 days before implantation. During this period, the zona pellucida detaches, allowing implantation to occur 5 to 7 days after fertilization..**

ART protocols for *in vitro* embryo culture and development attempt to recapitulate the timing and conditions of these events, albeit in an incredibly simplified fashion. The development of sequential media has allowed embryos to be grown *in vitro* up to 5 to 6 days after oocyte retrieval. After *in vitro* development, an embryo or multiple embryos are transferred into the cavity of the uterus. Criteria for embryo morphology—including cell number, symmetry, fragmentation, and granularity—are used in most centers to judge the quality of a particular embryo. However, these methods of assessment do not necessarily correlate well with genetic or embryonic developmental potential (441).

In an effort to better assess and select for transfer those embryos that will result in successful pregnancy, investigators have evaluated the advantages of extending the *in vitro* embryo culture period before transfer. *In vitro* culture to day 5 postretrieval allows the evaluation and selection of embryos at the blastocyst stage. It is likely that this extended culture does, in fact, increase the ability to judge appropriately the quality of an embryo. For instance, grading of the blastocyst according to the morphology of the inner cell mass

and trophectoderm has been correlated with implantation and pregnancy rates (442). Because of its increased implantation rate, extended embryo culture offers the advantage of limiting the number of transferred embryos while maintaining pregnancy rates. The true value of blastocyst transfer may therefore lie in its potential to decrease the rates of high-order multiple gestation resulting from ART. There appears to be an increased risk for monozygotic twinning of embryos cultured to the blastocyst stage (443), although this finding is currently being debated.

Pregnancy rates resulting from blastocyst transfer range between 44% for low-scoring blastocysts and 87% for top-scoring ones. Another predictor of the success rate of day 5 transfer is the number of eight-cell embryos on day 3 (443). Extended culture to

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the blastocyst stage (day 5) has been advocated by some to be beneficial for all IVF patients, with overall pregnancy rates of up to 43.8% (442,444). Others recommend it only if there are three or more eight-cell embryos on day 3 of *in vitro* culture (444). The application of extended embryo culture and blastocyst transfer requires laboratory specialization; therefore, the practice is institution specific.

Technical Aspects of Embryo Transfer

Despite its theoretic simplicity, transcervical embryo transfer into the intrauterine cavity is a procedure that requires significant skill. Correct performance of the procedure is thought to exert a significant impact on clinical outcome. Apart from the skill and experience of the operator, variables such as aspiration of cervical mucus (445), visualization by ultrasound guidance (446), duration of supine position immediately after embryo transfer (447), and type of bacteria cultured from the transfer catheter-tip postprocedure (448) have all been suggested to affect pregnancy outcomes. Microbial contamination of the embryo transfer is especially relevant because it may be prevented by antibiotic prophylaxis at the time of oocyte retrieval and careful handling of the catheter. Pregnancy rates are reduced by half in women with positive catheter-tip cultures (449).

Many different types of catheters have been used to perform embryo transfers, including hard catheters (*Erlangen, Tefcat, Tom Cat, Norfolk*) and soft catheters (*Frydman, Wallace*). The Frydman and Wallace catheters are thought to be less traumatic to the endometrium. However, no catheter has been shown to be definitively superior (450,451).

In women with a history of tubal disease, the difficulty of embryo transfer has

been associated with an increased risk of ectopic pregnancy (452). The number of transfer attempts, the time required for embryo transfer procedures, and the presence of blood inside the transfer catheter after the procedure do not affect clinical outcomes (453). In a series of more than 800 consecutive embryo transfer procedures, 85.9% were easy, 8.4% were difficult, 3.2% needed to be repeated, and 2.5% required cervical dilation. Technical difficulties, repeated embryo transfers because of retained embryos, and cervical dilation for stenosis did not affect the pregnancy rates in this study (454). The timing of the correction of cervical hindrances to embryo transfers may be important. Specifically, although it markedly facilitated the embryo transfers itself, cervical dilation at the time of oocyte retrieval in patients with a history of very difficult embryo transfer was associated with poor pregnancy outcome (1 in 41 cycles) (455). In contrast, surgical treatment of anticipated problems before commencement of IVF/embryo transfer yields good pregnancy rates. For example, hysteroscopic examination of the cervical canal may reveal a ridge, which can be resected (456). Alternatively, transcervical placement of a Malecot catheter at the time of hysteroscopy has been successful in allowing facile entry into the uterine cavity during subsequent embryo transfer or IUI. The Malecot catheter can be left in place for several weeks after hysteroscopy while the patient is maintained on *doxycycline* 100 mg twice daily. It is easily removed using gentle traction in the office as the day of embryo transfer approaches (457). Good clinical pregnancy outcomes have been reported for both techniques.

Cryopreservation of Embryos

The success of modern ovulation induction and fertilization regimens often results in embryos in excess of the number appropriate for transfer in a single treatment cycle. Cryopreservation of these embryos permits embryo transfer to the same patient in unstimulated cycles in the future. Some patients receive cryopreserved embryos during "natural" cycles, whereas other patients undergo endometrial preparation with sequential administration of exogenous estrogen and progesterone. Either regimen is significantly less expensive than a gonadotropin-stimulated cycle. More importantly, the risks of surgical complications and OHSS are nonexistent in cycles using cryopreserved embryos. Therefore, **pregnancies resulting from transfer of cryopreserved embryos effectively reduce the costs of pregnancy per ovulation stimulation. Conversely, in cryopreserved cycles, not all embryos survive**

thawing, and the pregnancy rates are lower than those using fresh embryos. In transfers of cryopreserved embryos using nondonor eggs (eggs from the intended recipient), 90% of

thawing procedures resulted in viable embryos for transfer. The rates of pregnancy and delivery were 22.2% and 20.4%, respectively, for cryopreserved embryo transfer procedures (413).

Pregnancy Testing and Follow-up of Early Pregnancy

The uncertainties surrounding ART treatment and its outcomes can be highly stressful, and treated couples are understandably anxious to obtain a pregnancy test as early as possible (458). **Serial quantitative hCG levels may be obtained starting on day 16 after oocyte retrieval. Serum hCG levels taken earlier than this day may give false-negative or false-positive results.** The latter may reflect the use of intramuscular hCG to trigger ovulation because this exogenous hCG can be detected for up to 14 days after injection (459). Day 16 serum quantitative hCG levels lower than 50 IU/L are associated with a 35% chance of an ongoing intrauterine pregnancy; levels greater than 500 IU/L are predictive of successful outcome in more than 95% of cases (460). **A single serum progesterone level on day 16 does not provide further prognostic value and is therefore not recommended..**

Patients usually undergo serial serum hCG level assessment early in pregnancy, followed by transvaginal ultrasound at 5 to 6 weeks of gestation to document intrauterine location of the pregnancy and the number of gestational sacs. This is especially important for patients with risk factors for ectopic pregnancy, those who are experiencing vaginal bleeding, and those at high risk for higher-order multiple gestation. In addition, such close follow-up in early pregnancy is both indicated and necessary among ART patients because an ongoing pregnancy requires patients to continue daily self-administration of supplemental progesterone (until the luteal-placental shift at about 9 to 10 weeks of gestation). **Transvaginal ultrasound at 7 to 8 weeks for identification of fetal cardiac activity can provide further reassurance..**

Success Rates

Success rates of IVF vary from program to program. Within a program, the rates of success vary with the patient's diagnosis and age. **The most comprehensive assessment of the efficacy of ART programs in North America comes from the database of the Society for Assisted Reproductive Technology (SART)** (413). The society's data collection began in 1985, and its annual summary is published in an effort to improve the quality of statistical reporting on ART. The database attempts to eliminate the effects of interprogram variation. The most recently published report of the society summarizes the results of ART in the United States and Canada for the year 2000, which are depicted in Table 30.10

(413). **Information on SART and registered ART clinics are accessible by the public at <http://www.sart.org>.** Significant improvements in overall ART outcomes have been made when compared with previously published results. In 2000, a 29.9% (28.4% in 1997 and 16.8% in 1992) rate of delivered pregnancies was reported per oocyte retrieval for standard IVF, with a cancellation rate of 14.3% (21.7% in 1997 and 15.4% in 1992), a pregnancy loss rate of 16.7% (18.1% in 1997 and 20% in 1992), and an ectopic pregnancy rate of 2.1% (0.9% in 1997 and 1.2% in 1992) per transfer. The delivered–pregnancy rate for cryopreserved embryo transfer was 20.4% in 2000 (18.8% in 1997 and 11.6% in 1992). Although the rates of birth defects did not appear to differ from those of the general population, the SART reporting system was not designed to specifically address this issue.

The age of the woman proved a significant determinant of success in ART (413)

(Table 30.11). Women aged 41 years and older had a delivery rate per retrieval of only 10.5%. The increase in cancellation rates with age—most likely the result of poor ovarian response—was consistent with significantly decreased ovarian reserve in older women. With the high efficacy of ICSI as a treatment for male factor infertility, the delivery rates per retrieval among couples with male factor infertility were comparable to those achieved in couples without male factor for a given female age group.

Table 30.10 Reported Outcomes for Assisted Reproductive Technology Procedures Performed in 2000 in the United States^a

	IVF	GIFT	ZIFT	Donor oocyte transfer ^b	CPE transfer ^c	CPEDO transfer	Host uterus transfer
No. of treatments ^a	73,406	549	763	7,581	13,083	2,721	1,210
Cancellations (%)	14.3%	10.9%	10.5%	8.6%	9.3%	9.2%	7.9%
No. of retrievals	62,881	489	683	6,929	NA	NA	1,114
No. of transfers	59,004	477	604	6,684	11,394	2,395	1,066
Transfers per retrieval	93.8%	97.5%	88.4%	96.5%	96.1%	96.9%	95.7%
No. of clinical pregnancies	22,567	162	242	3,413	2,906	704	459
Rate of pregnancy loss	16.7%	25.3%	15.7%	14.4%	20.0%	20.0%	16.8%
No. of deliveries	18,793	121	204	2,920	2,324	563	382
Deliveries per retrieval (%)	29.9%	24.7%	29.9%	42.1%	19.6%	22.8%	34.4%
Deliveries per transfer (%)	31.9%	25.4%	33.8%	43.7%	20.4%	23.5%	35.8%

Singleton delivery (%)	64.6%	71.9%	66.2%	59.6%	74.4%	71.0%	62.6%
No. of ectopic pregnancies	463	1	8	42	63	15	4
Rate of ectopic pregnancy (%)	2.1%	0.6%	3.3%	1.2%	2.2%	2.1%	0.9%

Note: CPE, cryopreserved embryos; CPEDO, cryopreserved embryos from donor oocytes; GIFT, gamele intrafallopian transfer; NA, not applicable; ZIFT=zygote intrafallopian transfer.

^aExept combination (n=326), research (n=41), and embryo banking (n=309) cycles.

^bIncludes known or anonymous but not host uterus or surrogate.

^cCryopreserved embryo transfer cycles not done in combination with fresh embryo transfers and not with donor egg or embryo.

^dIncludes all cycles, regardless of age and cause of infertility.

From ASRM/SART registry 2000 results. Fertil Steril 2004;81:1207-1220, with permission

Table 30.11 In Vitro Fertilization Procedures by Maternal Age Group and Infertility Diagnosis

IVF procedures (with and without ICSI) by age group and cause of infertility when there is no male factor infertility

<i>2000 IVF procedures</i>	<i>No. of retrieval</i>	<i>Canceled cycles (%)</i>	<i>Transfers per retrievals (%)</i>	<i>No. of pregnancies</i>	<i>No. of deliveries</i>
Age of women					
Women <35	17,712	10.3%	94.4%	7,422	6,495
Women 35-37	9,121	14.9%	94.2%	3,473	2,901
Women 38-40	7,582	20.1%	93.4%	2,308	1,761
Women >40	5,022	25.3%	90.1%	896	528

IVF, in vitro fertilization. From ASRM/SART registry 2000 results. Fertil Steril 2004;81:1207-1220.

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Treatment with Donor Oocytes

Women with premature ovarian failure have very few reproductive options. The use of donor oocytes may represent the only proven method by which most of these patients can become pregnant. Other patients to be considered for donor oocyte technology may include those with poor oocyte quality (including some patients with failed fertilization), those with poor ovarian response to stimulation, and those with a history of multiple failed ART cycles. Using embryos fertilized from donor eggs in 418 fresh embryo transfers involving 276 recipients, pregnancy and delivery rates were 36.2% and 29.3%, respectively. The cumulative pregnancy rate after four cycles reached 87.9% (461).

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Treatment with donor oocytes is available in many ART programs. **The method of donor selection is an important consideration.** Some patients may wish to find their own donor in a sister or friend. Others may choose to use an agency to identify a donor, who can remain anonymous. Although some ART programs may choose to be excluded from the matching process, most will assume the responsibility of screening the donor for medical, reproductive, and psychological fitness. **Like semen donors, potential oocyte donors must be stringently assessed, including screening for transmittable infectious or genetic diseases. Unlike semen, however, oocytes cannot presently be cryopreserved and quarantined.** Hence, the risk for transmission of infectious agents cannot be completely averted. Moreover, because oocyte donation involves COH, a donor is exposed to the same intensive monitoring and significant potential complications inherent to this intervention. Potential donors must be provided with detailed educational information, and meticulous informed consent is mandatory. In addition to undergoing medical screening, oocyte donors are subjected to a comprehensive psychosocial evaluation before being accepted as program participants. Even with such extensive screening and preparation, there is a significant dropout rate for both anonymous and directed oocyte donors (462). Because many potentially litigious issues arise in the administration of such a program, legal counsel is important in the management of an ovum donation center.

Considerable coordination is required to ensure that the recipient's endometrium

is appropriately prepared when embryos freshly fertilized from the donor oocytes are ready to be transferred (463). Regimens for ovulation induction and oocyte retrieval for the oocyte donor follow those of standard IVF protocols (Fig. 30.7.). Although the oocyte donor is exposed to many of the adverse effects of COH protocols (OHSS, postoperative pelvic discomfort, surgical and anesthesia risks, and medication side effects), her risk for multiple gestation and ectopic pregnancy can be virtually eliminated if she abstains from intercourse during her stimulation cycle.

To ensure adequate endometrial preparation, many recipients of donor oocytes are taken through a "mock" cycle before their actual treatment cycle. During the mock cycle, all hormonal agents are administered, and endometrial adequacy is documented by timed endometrial biopsies. The impact that the completion of a mock cycle might have on the pregnancy rates of subsequent ART cycles with donor eggs has not been studied in a randomized trial. However, such a cycle allows assessment of important factors such as patient compliance, histologic evidence of endometrial response to exogenous hormones, and the ease of embryo transfer (464). Many regimens for endometrial preparation have been described, although successful pregnancies have also been reported after embryo transfer in natural cycles. **Following is a typical regimen for endometrial preparation in recipients of donor oocytes:.**

- **If the recipient has no baseline ovarian function, no downregulation or baseline testing is required. However, if the recipient has endogenous ovarian function, GnRH agonist is started on day 21 in the luteal phase of the previous cycle. At onset of menses, downregulation is confirmed by the presence of serum estradiol levels of less than 50 pg/mL or an ultrasound examination documenting absence the of ovarian cysts. Once downregulation is confirmed, the dose of GnRH agonist is reduced..**

- **Start *estradiol* administration (*Estraderm* patches 0.2 mg every 48 hours, or *Vivelle* patches 0.2 mg every 48 hours, or *Estrace* 1.0 mg orally once per day)..**

- **Monitor serum estradiol levels every 3 to 7 days and adjust dosage to maintain serum estradiol levels of 150 to 300 pg/mL or continue fixed dose..**

- **Continue *estradiol* supplementation for at least 21 days at dosages that maintain**

these estrogen levels..

- **The progesterone start day is scheduled according to the day of embryo transfer (in a therapeutic cycle) or the day of endometrial biopsy (in a mock cycle)..**

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- **Start progesterone administration, 25 to 50 mg intramuscularly (day 1), then increase to 50 to 100 mg/day intramuscularly the following day..**
- **Discontinue GnRH agonist administration on day 2 of *progesterone* use..**
- **Mock cycle: Perform endometrial biopsy 10 to 12 days after *progesterone* is started. Therapeutic cycle: Perform embryo transfer on day 4 of *progesterone* use..**
- **Measure quantitative hCG 16 days or more after the date of donor oocyte retrieval..**

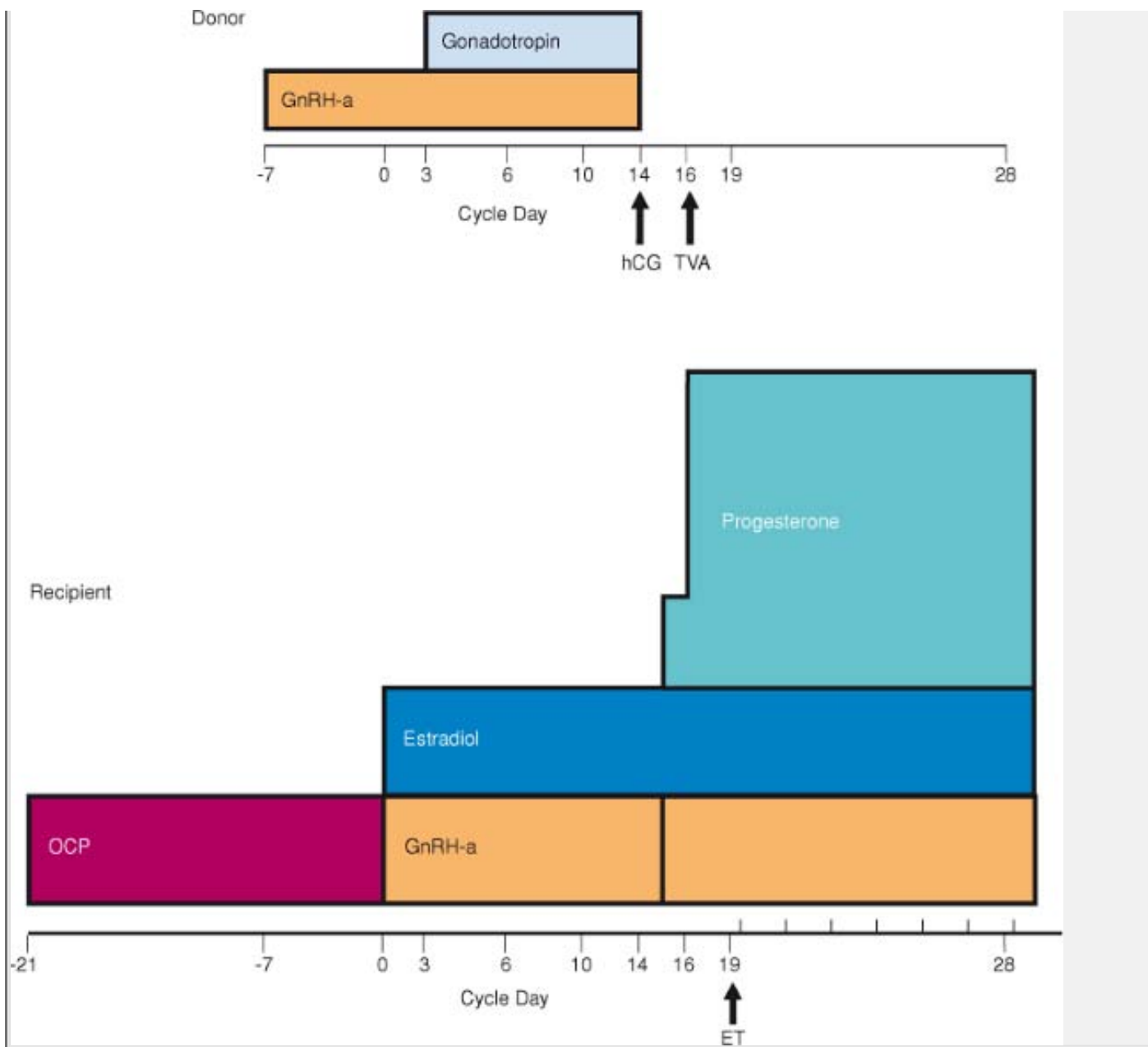


Figure 30.7 Regimens of ovarian stimulation and hormone replacement used to synchronize the development of ovarian follicles in the oocyte donor and the endometrial cycle in the recipient. (hCG, human chorionic gonadotropin; OCP, oral contraceptive pill; GnRH-a, gonadotropin releasing hormone antagonist; TVA, ultrasound-guided transvaginal aspiration of oocytes) (Adapted from *Chang PL, Sauer MY. Assisted reproductive techniques. Stenchever MA, ed. Atlas of clinical gynecology, Mishell DR, ed, Reproductive endocrinology. Vol. 3. Philadelphia, PA: Current Sciences Group, 1998, with permission.*).

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Many controversial issues and much ethical debate surround oocyte donation. Donors' expectations regarding the process itself, the quality of their medical care, and their level of involvement in decisions can be addressed by a conscientious ART team (465). Other topics, such as methods of donor recruitment and amounts of financial compensation, are much more challenging issues (466,467). Further effort is warranted to help clarify these issues and provide access to this highly efficacious ART treatment.

Complications of Assisted Reproductive Technology

Multiple Gestation

Multiple gestation, especially higher-order multiple gestation, is a serious complication of infertility treatment and has tremendous medical, psychological, social, and financial implications. In recent years, it has been reported that only 20% of higher-order multiple gestations are the result of spontaneous conceptions. The remaining 80% are attributable to reproductive interventions. Of these multiple gestations, one half are attributable to ART and one half to the use of ovulation drugs in non-ART cycles (468). Because the average age of women attempting pregnancy has risen during recent decades and increased maternal age affects the incidence of multiple gestation, rates of higher-order multiple gestation must be adjusted for maternal age when compared over time (469). For decades before 1971, higher-order multiple gestation occurred at a maternal age-adjusted incidence of about 30 per 100,000 live births from spontaneous conceptions (469,470). This incidence rose to 173.6 per 100,000 live births in 1997 (469) (Table 30.12). Because higher-order multiple gestations are predominantly triplets (91.2% were triplets in 1997) (468), this rate represents 6,737 triplets born in the United States in 1997 alone

(Table 30.13).

Significant medical risks accompany higher-order multiple gestation. There is an increased incidence of potentially life-threatening obstetric conditions such as acute fatty liver (471) and severe preeclampsia (472). The rate of fetal death during the third trimester is also unacceptably high at almost 17% (473). Obstetrically, triplets are at increased risk for preterm birth, low birth weight (<2,500 g), and very low birth weight (<1,500 g) compared with singletons or twins (474,475). When adjusted for gestational age at birth,

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triplets have the same rates of neonatal morbidity and mortality as twins and singletons (476,477), but triplets typically deliver much earlier. One notable exception is that preterm triplets are at significantly greater risk of severe retinopathy of prematurity, even when they are delivered at the same gestational age as a matched singleton or twin (477). Because of the extensive obstetric and neonatal intensive care required in higher-order multiple gestation pregnancies, enormous expenditures are required to provide medical care to these families (478). Finally, although not fully described, the immediate and long-term emotional and psychological impact on the mother, her partner, and the family unit, including other siblings, is likely to be daunting.

Table 30.12 Rate^a of Triplet and Higher-order Multiple Births, by Mother's Age; United States, 1980–1997

<i>Triplet and Higher-order Multiple Births</i>		
<i>Age group (yr)</i>	<i>1980</i>	<i>1997</i>
<20	14.8	20.7
20–24	31.4	46.8
25–29	42.8	151.0
30–34	58.3	293.6
35–39	47.6	403.2
40–44	b	315.4
45–49	b	2,100.2
All ages	37.0	173.6

^aPer 100,000 live-born infants.

^bNumbers do not meet standards of reliability or precision.

From **Centers for Disease Control and Prevention**. Contribution of assisted reproductive technology and ovulation-inducing drugs to triplet and higher-order multiple births—United States, 1980–1997.

MMWR Morb Mortal Wkly Rep 2000;49:535–538, with permission.

Table 30.13 Contribution of Assisted Reproductive Technology (ART) to Triplet and Higher-order Multiple Births (\geq Triplets)—United States, 1989–1997

Year	Total No. Live-born Infants ^a	No. of \geq Triplets	Percentage of \geq Triplets of Total No Live-born Infants		Percentage of \geq Triplets by Spontaneous Conception Using ART		Estimated Percentage of \geq Triplets Using Ovulation Drugs
			No. of \geq Triplets	Ratio ^b	Spontaneous Conception	Using ART	
1989	4,040,958	2,798	0.07	69.2			
1990	4,158,212	3,028	0.07	72.8		22.0 ^c	
1991	4,110,907	3,346	0.08	81.4		22.0 ^c	
1992	4,065,014	3,883	0.09	95.6			
1993	4,000,240	4,168	0.10	104.2			
1994	3,952,767	4,594	0.12	116.2			
1995	3,899,589	4,973	0.13	127.2			
1996 ^d	3,891,494	5,939	0.15	152.6	20.9	38.7	40.4
1997 ^d	3,880,894	6,737	0.17	173.6	18.4	43.4	38.2

^aData source is from Martin, et al. (468).

^bNumber of triplets per 100,000 live-born infants.

^cBased on number of ART-associated triplets and total number of triplets, 1990 and 1991.

^dPercentage of triplets by spontaneous conception, percentage of triplets using ART, and estimated percentage of triplets using ovulation drugs add up to 100% overall triplet ratio.

From **Centers for Disease Control and Prevention**. Contribution of assisted reproductive technology and ovulation-inducing drugs to triplet and higher-order multiple births—United States, 1980–1997. *MMWR Morb Mortal Wkly Rep* 2000;49:535–538, with permission.

To ameliorate this trend in higher-order multiple gestations, a number of medical and nonmedical causes are being identified. Non-ART COH with gonadotropins is a highly efficacious and commonly used treatment modality for infertile couples. It is significantly less expensive than ART and thereby more accessible to many patients. Unfortunately, it is associated with a 20% incidence of twin gestations and 10% incidence of higher-order multiple gestation (49). Current monitoring protocols for non-ART COH based on assessment of serum estradiol levels and the number of large follicles detected by ultrasound cannot entirely predict the risk for higher-order multiple gestation (479). **The risk for higher-order multiple gestation is significantly increased with younger age, peak serum estradiol levels greater than 1,385 pg/mL, and a total number of follicles of seven or more** (479). It is difficult to discern the significance of this latter measurement, however, because total follicle number depends on which follicles are measured, and it is unclear what should be the smallest reportable size. Further, a high total number of follicles may result from overstimulation of a patient with normal ovaries but unexpectedly high ovarian response or from treatment of a patient with PCO-like ovaries. Because the prevention and management strategies would differ for these two conditions, further stratification of patients and characterization of the COH cycles may clarify relative risks and direct efforts to more effectively prevent OHSS and multiple gestation. Suggestions to

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reduce higher-order multiple gestation in non-ART COH are being explored. None is without cost. One option would promote lowering the dosage of gonadotropins used in COH to aim at a lesser degree of ovarian response. This approach will almost certainly lower pregnancy rates. An alternative would be fewer interventions with non-ART COH and substitution with ART. In ART, the rate of higher-order multiple gestation is determined by the number of embryos transferred, not the ovarian response, which allows greater control of the higher-order multiple gestation rate. This approach would require a dramatic change in the guidelines for insurance company reimbursement of infertility treatments, however, or would necessitate the financing of such treatment by the couple. Currently, there are no accepted criteria guiding when a non-ART cycle should be canceled in an attempt to reduce the risk for higher-order multiple gestation. Informed recommendations for such standardization would be helpful.

More progress is being made toward reduction of higher-order multiple gestation in ART. One approach, discussed under "Embryo Transfer," would involve broader use of extended embryo culture, in which embryos are allowed to grow to the blastocyst stage *in vitro*. Blastocysts have been shown to have greater developmental potential and higher

implantation rates than day 3 embryos, so that even if fewer (a maximum of one to two) blastocysts are transferred, pregnancy rates remain high (442). Another approach would follow the lead of countries outside the United States that have defined set limits for the maximum number of embryos transferred in a given ART cycle. The American Society of Reproductive Medicine has recently addressed this issue by publishing guidelines for embryo transfer during ART. **Briefly, a maximum of two, three, and four embryos can be transferred to women with above-average prognosis (age <35 years), average prognosis (age between 35 and 37 years), and below-average prognosis (age 38–40 years) respectively** (480). In donor oocyte cycles, the age of the donor (not the recipient) should be used to determine the number of embryos to be transferred. Data on the efficacy of this protocol are expected to be available in a few years. **Others have advocated similarly stringent guidelines, promoting the transfer of a maximum of two embryos in ART cycles to minimize the risk for higher-order multiple gestation** (481). Cryopreservation of excess embryos should be encouraged to promote more cycles involving transfer of cryopreserved embryos. Universal application of such changes will force patients and doctors to emphasize cumulative birth rates rather than pregnancy rate per cycle. By focusing on cumulative birth rates, patients can have more realistic expectations, and the demand to have an excessive number of embryos transferred would decrease (482,483). As discussed for non-ART COH, these changes will involve alterations in the entire financial reimbursement structure for ART services. There is no doubt that this approach will present many challenges.

Other factors contributing to the increased rates of higher-order multiple gestation have been identified. It has been suggested that government-mandated annual reporting of clinic-specific pregnancy rates places undue emphasis on pregnancy rate per cycle. This may encourage the promotion of higher pregnancy rates at the expense of higher multiple pregnancy rates. If the goal of infertility therapy is the delivery of a healthy baby, both pregnancy rates and incidence of multiple gestation must be considered in determining treatment efficacy. Financial reimbursement schedules by insurance companies, lack of federal support for IVF research, and insufficient patient education regarding the true risk for higher-order multiple gestation are all being examined (484,485,486,487).

On the scientific front, new technologies, such as **preimplantation genetic diagnosis, may ultimately eliminate the risk of higher-order multiple gestation. Preimplantation genetic diagnosis is a clinical diagnostic procedure that can be performed on the embryo itself to determine whether a particular genetic abnormality is present before its transfer into the uterus** (488). Preimplantation genetic diagnosis has been developed in an effort to improve the chances of having healthy infants in families at high risk for a particular genetic disease. It is most frequently performed using blastomere (a cell from a

day 3 embryo containing six to eight cells) biopsy, followed by genetic testing on the cell obtained. The technique chosen for diagnostic testing depends on the type of genetic defect being investigated. For example, fluorescence *in situ* hybridization (FISH) can be used to assess aneuploidy, translocation, and other structural chromosomal defects (489). This technique can also be used to exclude transmission of X-linked diseases by identification of X and Y chromosomes, thus allowing transfer of only female embryos (490). Alternatively, familial single gene mutations can be identified by extracting blastomere DNA, followed by polymerase chain reaction, restriction enzyme digest, or sequencing. In a recent study involving 262 ART cycles, the embryos obtained from women with a poor prognosis (characterized by age older than 35 years with previous IVF failures and karyotypic defects) were randomized to preimplantation genetic diagnosis for aneuploidy or a control procedure. Those chromosomes commonly involved in aneuploidies (X, Y, 13, 14, 15, 16, 18, 21, and 22) were assessed using FISH in the study group. Although fewer embryos were transferred in the group undergoing preimplantation genetic diagnosis, higher clinical pregnancy rates (37% versus 27%) and implantation rates (22.5% versus 10.2%) were reported when compared with controls (491). Preimplantation genetic diagnosis may assist in the selection of euploidic embryos, thereby offering tremendous potential in the effort to reduce the risk of higher-order multiple gestation.

As progress is being made to eradicate the complication of higher-order multiple gestation, others have suggested ways to reduce subsequent risks once higher-order multiple gestation has occurred. **One option for preventing some of the maternal and fetal complications of higher-order multiple gestation involves the judicious use of selective pregnancy termination or multifetal reduction.** Although any higher-order multiple gestation is a candidate for this procedure, the reduction of triplet to twin pregnancies is most common and best studied. Overall, about 14% of triplet pregnancies reduce spontaneously to twin pregnancies after fetal heart activity is documented on transvaginal ultrasound at 8 to 9 weeks of gestation (492,493). Although some studies have not found multifetal reduction to result in significant improvement in gestational length or intrauterine growth restriction (493,494), many centers have reported improved outcomes after reductions to twin gestations. Twin gestations after reduction have similar outcomes when compared with spontaneous twin gestations (495,496). Reduction of triplet to twin gestation has been reported to decrease the risk for preterm birth (497), low birth weight (497), preeclampsia (496), and delivery before 36 weeks (496). Specifically, the rates of preterm birth before 28, 32, and 34 weeks of gestation, as well as birth weights of less than 1,000, 1,500, and 2,000 g, were significantly lower in

twins after reduction from triplet pregnancy compared with triplets who did not undergo reduction (498). However, any benefits achieved for newborn health often incur tremendous emotional, psychological, and physical costs. **The major complications of fetal reduction include a 13% risk for premature rupture of the membranes for triplet to twin reduction** (499). There is a 5% to 10% risk of losing the entire pregnancy (500) after reduction has occurred. Further, major depression occurs in 80% of women who lose the pregnancy as a complication of fetal reduction and in one third of women who have live twins after fetal reduction (501).

Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome is a medical complication that is both completely iatrogenic and unique to the treatment of infertility. Although the pathophysiology of OHSS is not well understood, the signs and symptoms of this disease can be attributed to local and systemic increase in capillary permeability. These changes, in turn, result in the depletion of intravascular volume at the expense of third-space fluid accumulation.

Ovarian hyperstimulation syndrome has been directly associated with increasing numbers of stimulated follicles and retrieved oocytes (502,503), the presence of PCOS (504,505,506), and high serum estradiol levels (502,507,508). Despite these associations,

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however, hyperestrogenemia is not currently thought to be the main cause of OHSS (509,510,511,512). Rather, the increased production of vasoactive substances—such as prorenin, renin, angiotensin-converting enzyme, angiotensin I, angiotensin II, and angiotensinogen—by the hyperstimulated ovaries has been implicated (513,514,515,516,517,518,519,520,521). Still, it remains possible that hyperestrogenemia, especially in the presence of hemoconcentration, has important effects on the thromboembolic risks demonstrated with OHSS.

Inflammatory responses are certainly present in OHSS patients, with possible roles for cytokines, histamine, and prostaglandins in the disease pathogenesis (522,523,524). In particular, the link between vascular endothelial growth factor (VEGF) and OHSS has been extensively studied. Vascular endothelial growth factor has been shown to exhibit a dose-related expression in human granulosa cells upon stimulation by hCG (525). Further, serum VEGF levels correlate with OHSS severity (526,527) demonstrating a sensitivity and specificity of 100% and 60%, respectively (527). The central role of an inflammatory response is supported by a number of other findings. For instance, mast cells are abundant

in ovulatory follicles (528), and histamine blockade has been reported to ameliorate and, in some cases, even prevent OHSS in animal models (523,529). Furthermore, it is clinically well recognized that allergy or hypersensitivity act as risk factors for the development of OHSS (502). To date, however, scientific evidence for these factors is still considered preliminary, and further investigation is warranted to clarify their true role in OHSS (512).

Recently, **a distinction between early- and late-onset OHSS has been described** (530). **Early OHSS, with onset arbitrarily set within 9 days of oocyte retrieval, is associated with higher serum estradiol levels and follicle numbers during COH. In contrast, late OHSS has onset more than 9 days after oocyte retrieval. Late-onset OHSS has been associated not with measures of follicular response, but with multiple gestation.** Early and late OHSS may even reflect somewhat distinct pathophysiologic mechanisms. It has been proposed that early OHSS may result from ovarian stimulation by the exogenous hCG given to trigger ovulation, whereas late OHSS may be more closely linked to the endogenous hCG produced when pregnancy ensues (530).

Ovarian hyperstimulation syndrome has a varied spectrum of clinical presentation.

An attempt to better understand this heterogeneity led to the development of a staging system for OHSS that would reflect symptom severity. **This classification categorizes patients according to mild, moderate, and severe disease** (531). In mild OHSS, patients often report mild abdominal distention and soreness, nausea, and vomiting. Ovarian enlargement can be 5 to 12 cm. Moderate disease is marked by the presence of abdominal ascites on ultrasound examination. Severe disease is diagnosed when there are clinical signs of tense ascites, hydrothorax, shortness of breath, hemoconcentration, hypercoagulability, or any complications of OHSS such as renal failure, thromboembolism, or acute respiratory distress syndrome (ARDS).

This classification may serve as a useful guide; however, its application may sometimes be misleading. For example, ovarian enlargement is common after COH and, by itself, is not informative. Furthermore, many patients experience mild pelvic soreness and abdominal bloating after COH, and their ovaries may be enlarged when viewed on transvaginal ultrasound. Whether these patients reflect an abnormal response to COH or merely represent a subset of normal responders is debatable. The fact that reported incidence of OHSS after COH has ranged from 7.3% (mild or moderate disease) and 4.2% (severe disease) to 33% overall may suggest that the staging system is itself open to interpretation (502,531).

Management of OHSS

Patients undergoing COH with or without ART should be educated about the signs and symptoms of OHSS. They should be instructed to contact their health care provider if they experience abdominal bloating, abdominal discomfort or pain, early satiety, nausea, vomiting, decreased urine output, or weight gain of more than 2 lb per day. Patients with these initial symptoms should be fully assessed to establish their

baseline condition for future comparisons, if that should become necessary. Pertinent points in the assessment of patients with OHSS are as follows: .

History:.

- **Age, history of OHSS in previous infertility treatment, history of PCOS.**
- **Characteristics of COH (dose of gonadotropins, number of follicles, number of eggs for an ART cycle, peak serum estradiol level, date of hCG administration, date of oocyte retrieval, date of embryo transfer, number of embryos transferred at embryo transfer).**
- **Onset of symptoms, their progression (stable versus rapidly worsening), and their severity.**

Specific questions should address the presence of the following symptoms: .

- **Abdominal discomfort, pain, bloating; increased abdominal girth; early satiety.**
- **Shortness of breath, chest pain.**
- **Nausea, vomiting.**
- **Weight gain (total amount gained since start of COH and pounds gained per day).**

- **Decreased urine output.**

A complete physical examination should be performed, with specific attention to the following areas:

- **Signs of hypotension, hemodynamic instability, and dehydration.**

- **Chest: evidence of pleural edema or effusion, congestive heart failure, limited chest expansion because of ascites.**

- **Abdomen: ascites (mild, moderate, tense), peritoneal signs.**

- **Peripheral exam: pitting edema.**

- **Pelvic exam is contraindicated because enlarged ovaries can be fragile and prone to torsion.**

The following investigations should be performed:

- **Complete blood count, prothrombin time, partial thromboplastin time, serum electrolytes, liver function tests, creatinine, blood urea nitrogen.**

- **Chest x-ray if there is significant shortness of breath or abnormalities on chest exam (shielding the pelvis can protect potential pregnancy from irradiation).**

- **Transvaginal ultrasound to document the baseline amount of ascites and size of ovaries.**

- **Documentation of oxygen saturation is indicated if there is evidence of**

respiratory compromise.

- **Serum hCG on day 16 after oocyte retrieval if embryo transfer has occurred.**

This initial assessment should enable the clinician to decide whether the patient with OHSS needs to be admitted to the hospital for observation and supportive care. Accepted indications for hospitalization include inability to tolerate oral hydration,

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hemodynamic instability, respiratory compromise, tense ascites, hemoconcentration, leukocytosis, hyponatremia, hyperkalemia, abnormal renal or liver function, and decreased oxygen saturation. If the diagnosis and its severity remain in doubt after initial assessment, it is reasonable to observe patients overnight while further assessing fluid balance and the presence of oliguria. The need for more prolonged hospitalization often becomes rapidly evident. The presence of peritoneal signs, such as abdominal rebound tenderness or guarding, in a patient with possible OHSS may indicate ovarian torsion, hemorrhage, or rupture of enlarged ovarian cysts. These signs may also represent those rare cases of postovocyte retrieval tubo-ovarian abscess. **Admission to the hospital is mandatory, and admission to an intensive care setting should be seriously considered, if the patient has complications of OHSS such as renal failure, ARDS, thromboembolic disease, or severe hydrothorax.**

The onset of OHSS soon after hCG administration or oocyte retrieval is associated with an increased risk for progression to severe disease. Pregnancy is also known to cause worsening of OHSS, most likely as a result of ovarian stimulation by endogenous hCG. Therefore, in cases of very early-onset OHSS, the benefits of withholding embryo transfer, cryopreserving these embryos, and performing embryo transfer in a future unstimulated cycle should be considered and discussed.

Outpatient Management

If outpatient management is appropriate, the patient should be instructed to limit her activity, to weigh herself daily, and to monitor her fluid intake (at least 1 L/day of mostly electrolyte-balanced fluid) and output. Daily follow-up by telephone or visit is important because the severity of OHSS may change at any time. The patient should contact her health care provider if she notes worsening of the symptoms or if her weight gain increases to more than 2 lb per day. Reassessment is indicated in these situations.

Inpatient Management

Inpatient management of patients with OHSS involves meticulous monitoring of vital signs and fluid balances as well as supportive care. This care includes use of intravenous hydration and prevention of complications such as thromboembolic prophylaxis, although more invasive interventions, such as paracentesis, may become necessary. Following is a typical inpatient protocol used for management of patients with moderate to severe OHSS: .

The initial assessment should be performed as outlined previously, accompanied by the following assessments: .

- **Vital signs (including oxygen saturation monitoring if respiratory compromise is present) every 4 hours initially.**
- **Fluid intake and output measurements.**
- **Daily weights and abdominal girth.**
- **Daily hematocrit, leukocyte count, serum electrolytes, renal function tests.**
- **Liver function tests, prothrombin time, partial thromboplastin time obtained on admission and repeated as necessary.**

Supportive Care: .

- **If hypotension or oliguria is present, a bolus of 1 L of normal saline should be given over 1 hour then maintained with D5 normal saline (or D5_{1/2} normal saline) at 150 mL/h.**
If hypotension or oliguria is not present, but the hematocrit is greater than 45%, maintenance with D5 normal saline at 150 mL/h should be initiated.

The maintenance rate for intravenous fluids can be lowered if the hematocrit is normal. Although administration of intravenous fluids will certainly lead to

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an increase in third spacing, it is important to maintain adequate intravascular volume and urine output. The hematocrit may need to be monitored twice a day initially; the intravenous fluid maintenance can be titrated downward as the hematocrit normalizes. This should help to minimize third-spacing side effects. Lactated Ringer's solution should not be used for intravenous hydration in patients with OHSS..

- **If oliguria persists, a small bolus of 250 to 500 mL of normal saline can be given to increase urine output.** The efficacy of *albumin* (or other plasma expanders) in the treatment or resolution of OHSS has not been studied in a prospective, randomized fashion. However, it is reasonable to attempt gentle diuresis in a patient who has normal blood pressure and hematocrit but in whom oliguria or weight gain persists. Diuresis may be accomplished using sequential administration of 50 mL of 25% *albumin* followed by *furosemide*, 10 mg given intravenously. This combination can be repeated 3 to 4 times per 24 hours as necessary. Serum sodium, potassium, and creatinine must be monitored closely when employing *albumin* or *furosemide* diuresis.

- **Small amounts of fluid can be taken orally.** As the OHSS improves, the amount of intake can be increased as the intravenous fluid maintenance decreases. During the resolution of OHSS, a maximum total input of 1 L/day has been recommended to prevent increases in third spacing (512).

- **Paracentesis is indicated if the patient has severe abdominal discomfort and respiratory compromise caused by large volumes of ascites.** Hydrothoraces have also been reported to resolve after paracentesis. The presence of massive ascites, combined with persistent oliguria or hypotension despite medical therapy, is also an indication for paracentesis because diuresis often results after the severe abdominal pressure is relieved. Both abdominal paracentesis under ultrasound guidance and transvaginal ultrasound-guided paracentesis are acceptable practices (532,533).

- **If embryo transfer has already been performed or is scheduled,**

progesterone supplementation should be given as indicated by the ART

protocol. Administration of progesterone is not thought to affect OHSS adversely.

However, pregnancy may cause worsening of OHSS as a result of the stimulation of the ovaries by increasing levels of endogenous hCG.

- **Antiemetics and analgesics (i.e., acetaminophen) can be given to relieve symptoms..**

- **Complications of OHSS, such as ARDS, thromboembolism, and renal failure, should be treated in an intensive care setting when indicated..**

Preventative Measures:

- **Hemoconcentration and severe leukocytosis are considered risk factors for thromboembolic disease in patients with OHSS (512). Therefore, heparin, (unfractionated or low molecular weight) should be considered for all patients with OHSS to prevent thromboembolism.** In addition, vascular support stockings should be used in ambulatory patients. Intermittent compression stockings should be used for patients who are not ambulating.

Prevention of OHSS

Because OHSS can potentially cause severe and sometimes life-

threatening complications, prevention is an essential consideration. When high estradiol levels (>3,000 pg/mL) are noted before hCG administration, prevention of OHSS can be attempted by coasting. Coasting involves withholding gonadotropin and delaying hCG until serum estradiol levels decrease or follicular diameter of greater than or equal to 18 mm is seen on transvaginal ultrasound (396,397,398). Coasting does not completely prevent severe OHSS or cycle cancellation, but it does minimize the risk for severe OHSS

while maintaining high pregnancy rates. An alternative strategy to minimize OHSS risk involves cryopreservation of embryos at the pronucleate stage and transfer of thawed embryos in a subsequent cycle using endometrial preparation without COH. The strategy of

cryopreservation results in excellent pregnancy and live birth rates comparable to similar cycles with fresh embryo transfer. The incidence of severe OHSS appears to be reduced, but more importantly, the duration of severe OHSS may be shortened when cryopreservation strategies are used (534,535,536).

Unfortunately, even with close monitoring and use of the lowest possible doses of gonadotropins during COH, it still may prove difficult to prevent OHSS. A novel strategy that may remedy these difficulties involves the *in vitro* maturation (IVM) of oocytes. Using IVM, immature follicles are aspirated and the retrieved oocytes are grown *in vitro* until mature. This is potentially advantageous because IVM completely obviates the need to stimulate the ovaries with gonadotropins. Once ICSI is performed on IVM oocytes, embryos are transferred to the uterus, which has been hormonally prepared. *In vitro* maturation is particularly applicable to women with PCOS, who have a known increased risk for OHSS and whose ovaries are characterized by multiple small follicles that can be aspirated in the absence of stimulation. *In vitro* maturation has been reported to yield pregnancy rates of 27.1% to 38% in women with PCOS (537,538,539). However, data on long term effects on fetal and postnatal development are not yet available.

Ectopic and Heterotopic Pregnancy

The incidence of ectopic pregnancy is 2% in the general population (540). However, its incidence is increased after ART and can be as high as 4% (541). The timing of embryo transfer (cleavage stage versus blastocyst stage) does not appear to influence the incidence (542). The main risk factors for ectopic pregnancy in IVF treatment are tubal factor infertility and, possibly, previous myomectomy (541). **The incidence of heterotopic pregnancy, which is normally rare, is particularly high (1%) after IVF treatment.** Multiple gestation and high hormonal levels during COH and early pregnancy have been suggested as possible causes. **It is important to have a high index of suspicion for the occurrence of heterotopic pregnancies because only 40% to 84% of cases can be diagnosed with transvaginal ultrasound at the initial presentation (543,544).** After treatment of the heterotopic gestation with laparoscopy, laparotomy, or ultrasound-guided injection of potassium chloride into the extrauterine pregnancy, the overall delivery rate for the intrauterine pregnancy is 66% (543).

Risk of Cancer after Fertility Therapy

The possibility that ovulation-inducing medications might promote the development of cancers

of the reproductive tract, specifically with regard to ovarian cancer, was introduced in the early 1990s (545). One theory behind this proposed risk is that ovarian cancer may arise, in some cases, as the result of damage to the ovarian epithelium during ovulation. Lactation, oral contraceptives, late onset of menarche, early menopause, and multiparity are known to protect against ovarian cancer. Moreover, each is associated with a reduction in the total lifetime number of ovulatory cycles. The lower risk of ovarian cancer in women with increased length of anovulation raised the question of whether dramatic increase in the number of eggs ovulated during superovulation therapy would, in turn, increase the risk of ovarian cancer. Alternatively, some believe that because gonadotropins (FSH and LH) increase cellular proliferation and division within ovarian follicles, their use might create a predisposition to cancer. Both of the most common hormonal therapies used for induction of ovulation — *clomiphene citrate* and *exogenous gonadotropins*—result in increased gonadotropin stimulation of the ovary. These therapies might, therefore, increase the incidence of ovarian cancer in treated infertility patients. Concern about this potential risk for cancer after fertility therapy has also been extended to other organs, including the uterus and breast.

Currently, several factors prevent an accurate calculation of the true risk for developing cancer of the breast, uterus, or ovary after treatment with ovulation-inducing agents. First, contemporary fertility treatments and their dosages remain relatively new and are usually

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used in women younger than 40 to 45 years of age. Because ovarian, uterine, and some breast cancers typically occur in older women, the number of patients who were treated with fertility drugs and are now in their middle to late 60s may still be too small to detect elevations in cancer risk. Second, it is hard to differentiate the effect of fertility treatment from the effect that being infertile itself might have on future development of malignancies of the breast, uterus, or ovary. Finally, most of the studies addressing these risks are clouded by small numbers, intake of a variety of medications, and recall bias. All these factors make the interpretation of data difficult (546).

Two of the more recent studies failed to attribute an increased risk for breast, uterine, or ovarian cancer to medications used for superovulation in the treatment of infertility (547,548). One study evaluated more than 20,000 women with exposure to fertility drugs used for IVF and compared them with nearly 10,000 infertile controls. The authors reported no overall increased incidence of uterine, breast, or ovarian cancers in women exposed to medications used for IVF (548). Two other interesting findings represent some of the limitations to these types of studies. **The authors reported that the risk of ovarian and uterine cancer was higher in women with unexplained infertility, regardless of**

whether they had received ovulation induction medications. This may suggest risks associated with the unexplained infertility itself, or the possibility of undiagnosed cancers causing infertility. In addition, the authors reported an increase in the risk of breast and uterine cancer only within the first year after receiving infertility medications for IVF. Patients undergoing IVF are followed closely and may, therefore, be more likely to report early signs or symptoms of these cancers to their physicians. Alternatively, rather than causing these cancers, fertility medications may only stimulate the growth and subsequent diagnosis of pre-existing tumors.

Psychological Support

Stress, as manifested by anxiety or depression, is thought to be increased in women experiencing infertility. The relationship between stress and infertility is complex and may represent a vicious cycle in which infertility results in stress, which results in further difficulty in conceiving (549,550,551). Results from a recent prospective, randomized trial support the value of group cognitive-behavioral therapy among infertile couples (552). This therapy uses a variety of approaches, including relaxation training such as yoga, cognitive restructuring, methods for emotional expression, and information on nutrition and exercise with respect to infertility. Although the mechanism by which relaxation therapies aid fertility is unknown and issues such as high dropout rates need to be addressed by further research, **the option of psychological support and counseling, on an individual or group basis, should be offered to patients experiencing infertility** (553).

Other Considerations

One of the most important aspects of the treatment of patients with subfertility or infertility is the process of deciding when no further treatment will be pursued. This crucial topic must be addressed early in infertility therapy. Patients must be accurately informed of estimated success rates and reasonable expectations for all therapeutic interventions. It is equally important to identify an end point to medical intervention at the outset of treatment. This end point offers patients a mental time frame in which they can make both medical and personal decisions. One viable alternative for many couples is adoption, although the process of adoption has become increasingly complex. **Many patients may want to simultaneously explore infertility therapy and adoption. The choice of which course to pursue is a very difficult decision that may be facilitated by both physician input and strong psychosocial counseling and support..**

Preservation of Fertility in Cancer Patients

Aside from helping subfertile couples build families, technologic advances in tissue and gamete cryopreservation, in combination with ART, have made future fertility possible for some men and women who are faced with surgery, radiotherapy, or chemotherapy for

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cancer treatment. **Sperm cryopreservation has become a widely available option to allow fertility preservation in young men whose cancer treatment may render them infertile.** The wide range of neoplastic disorders for which sperm cryopreservation have been successful include leukemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and testicular cancer (554). Although most patients with these disorders are systemically ill and therefore exhibit decreased total motile sperm counts when compared with patients who do not have cancer, fewer than 20% have azoospermia, and cryopreservation is possible in most patients (554). Further, cryopreserved sperm from cancer patients tolerate thawing as well as samples obtained from patients without cancer (555).

Unfortunately, the efficacy of oocyte cryopreservation lags behind that of sperm preservation. Married women who are scheduled to undergo sterility-inducing cancer treatments may take the option of completing an IVF cycle so that oocytes can be fertilized and the resulting embryos can be cryopreserved for transfer later in life. However, an IVF cycle may require 2 weeks to complete, rendering this option unrealistic for patients in whom a delay in cancer treatment would compromise their prognosis. Even patients who are able to undergo IVF treatment usually do not have the time necessary for use of a downregulation protocol. Consequently, these women are usually prescribed the shorter, flare protocol, which may give suboptimal response (431). Use of GnRH antagonists may offer a special advantage in this situation. These agents can induce hypothalamic-pituitary downregulation after being started on day 6 of gonadotropin treatment, which obviates the need for the more time-consuming use of GnRH agonists (556).

Patients who are single or who have medical contraindications to IVF treatment may be candidates for ovarian tissue cryopreservation. Ovarian cortical biopsy specimens containing numerous primordial follicles have been successfully retrieved by a laparoscopic approach in healthy volunteers and in cancer patients (557,558,559). **It remains to be determined whether this promising technology creates a risk for reintroduction of malignant cells after autotransplantation of ovarian tissue and whether thawed immature oocytes should be used in *in vitro* maturation protocols..**

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31

Recurrent Pregnancy Loss

Laura Fox-Lee

Daniel J. Schust



- **Isolated spontaneous pregnancy loss is remarkably common. Recurrent pregnancy loss (RPL) affects between 1 in 300 and 1 in 100 couples.**
- **After several pregnancy losses, the chance of having a viable birth is greater than that of having another loss, even without treatment. Prognosis can improve dramatically with treatment of a known underlying cause of RPL.**
- **Parental chromosomal abnormalities and antiphospholipid antibody syndrome (APAS) are the only undisputed causes of RPL. Other well-described causes include anatomic, endocrine, thrombotic, and possibly other immunologic factors.**
- **The state of coagulability is a fine balance between pro- and antithrombotic pathways. The hypercoagulability of pregnancy can be largely attributed to increases in prothrombotic factors and decreases in those that inhibit coagulation.**
-

The immunologic interactions at the maternal–fetal interface reflect the presence of unique cellular constituents combined with the actions of steroid hormones, protein hormones, and metabolic factors.

- **Evaluation of patients with RPL should include a detailed patient and family history, an examination focusing on endocrine and anatomic abnormalities, and laboratory studies limited to evaluating treatable etiologies.**

- **Early pregnancies in patients with RPL should be monitored with ultrasound examinations, assessment of β -human chorionic gonadotrophin (hCG) levels if indicated, and frequent visits with psychological support. In the event of pregnancy loss, tissues should be obtained for karyotype analysis.**

- **In treating RPL, there is evidence to support repairing anatomic abnormalities, correcting pre-existing endocrine disorders, and treating APAS and other thrombophilic disorders.**

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Advances in the ability to document and diagnose early pregnancy have revealed that spontaneous pregnancy loss is a common event. Spontaneous pregnancy loss is, in fact, the most common complication of pregnancy. Approximately 70% of human conceptions fail to achieve viability, and an estimated 50% are lost before the first missed menstrual period (1). Most of these pregnancy losses are unrecognized. Studies using sensitive assays for human chorionic gonadotropin (hCG) indicate that the actual rate of pregnancy loss after implantation is 31% (2). Of pregnancies that are clinically recognized, loss occurs in 15% before 20 weeks of gestation (from last menstrual period) (3,4).

Traditionally, recurrent abortion has been defined as the occurrence of three or more clinically recognized pregnancy losses before 20 weeks from the last menstrual period. Using this definition, recurrent pregnancy loss (RPL) occurs in approximately 1 in 300 pregnancies (2). Clinical investigation of pregnancy loss, however, may be initiated after two consecutive spontaneous abortions, especially when fetal heart activity is identified before any of the pregnancy losses, when the woman is older than 35 years of age, or when the couple has had difficulty conceiving. If clinical intervention is undertaken in the form of investigation after two spontaneous abortions, approximately 1% of pregnant women will require evaluation (3). Even with a history of RPL, a patient is more likely to carry her next pregnancy successfully to term than to miscarry. **For patients with a history of RPL, the risk of subsequent pregnancy loss is estimated to be 24% after two clinically recognized losses, 30% after three losses, and 40% to 50% after four losses (5).** These data make clinical study of RPL and its treatment difficult because very large groups of patients must be studied to demonstrate the effects of any proposed therapeutic intervention.

Etiology

Parental chromosomal abnormalities and thrombotic complications of the antiphospholipid antibody syndrome (APAS) are the only undisputed causes of recurrent abortion. However, collectively these abnormalities account for less than 10% to 15% of RPLs. Although the exact proportion of patients diagnosed with a

particular abnormality may vary among the populations studied, other associations have been made with anatomic abnormalities (12%–16%), endocrine problems (17%–20%), infections (0.5%–5%), and immunologic factors, including those associated with the APAS (20%–50%). Other miscellaneous factors have been implicated and account for approximately 10% of cases. Even after a thorough evaluation, however, the potential cause remains unexplained in about one third to one half of cases (3,6) (Table 31.1).

Genetic Factors

The most common inborn parental chromosomal abnormalities contributing to recurrent abortion are balanced translocations (7,8,9). In balanced translocations, one parent carries an overall normal gene content but has a piece of one chromosome inappropriately attached to another. Depending on the nature of the translocation (reciprocal or Robertsonian), the gametes produced by the translocation carrier will be normal (reciprocal only), balanced, or unbalanced for the translocated DNA. If fertilized by a chromosomally normal gamete, the resulting embryo may be chromosomally normal (reciprocal only) or may be a balanced or unbalanced carrier of the translocation. Most gametes and embryos with abnormal chromosomal status will not survive. Of those that do survive, live offspring will either be carriers of a balanced translocation or, for Robertsonian translocations, be monosomic or trisomic for the translocated chromosomal DNA.

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Among the possible chromosomal monosomies, only that of the X chromosome typically permits viable offspring. On careful examination, however, many of these offspring may exhibit mosaicism. Embryonic chromosomal monosomy may be particularly prevalent among patients with histories of RPL who are undergoing *in vitro* fertilization (10). Compared with monosomies, chromosomal trisomies (e.g., trisomy 13, 18, and 21) appear to be more readily tolerated, although mosaicism may be implicated with these abnormalities as well.

Table 31.1 Proposed Etiologies for Recurrent Spontaneous Abortion

<i>Etiology</i>	<i>Proposed Incidence</i>
Genetic factors	3.5%–5%
1. Chromosomal	
2. Single gene defects	
3 Multifactorial	
Anatomic factors	12%–16%
1. Congenital	
a. Incomplete mullerian fusion or septum resorption	
b. DES exposure	
c. Uterine artery anomalies	
d. Cervical incompetence	
2. Acquired	
a. Cervical incompetence	
b. Synechiae	
c. Leiomyomas	
d. Adenomyosis	
Endocrine factors	17%–20%

1. Luteal phase insufficiency	
2. Polycystic ovarian syndrome, including insulin resistance and hyperandrogenism	
3. Other androgen disorders	
4. Diabetes mellitus	
5. Thyroid disorders	
6. Prolactin disorders	
<i>Infectious factors</i>	0.5%–5%
1. Bacteria	
2. Viruses	
3. Parasites	
4. Zoonotic	
5. Fungal	
<i>Immunologic factors</i>	20%–50%
1. Cellular mechanisms	
a. Suppressor cell or factor deficiency	
b. Alterations in major histocompatibility antigen expression	
c. Alterations in cellular immune regulation	
1. Th1 immune responses to reproductive antigens (embryo or trophoblast)	
2. Th2 cytokine or growth factor deficiency	
3. Hormonal-progesterone, estrogen, prolactin, androgen alterations	
4. Tryptophan metabolism	
2. Humoral mechanisms	
a. Antiphospholipid antibodies	
b. Antithyroid antibodies	
c. Antisperm antibodies	
d. Antitrophoblast antibodies	
e. Blocking antibody deficiency	
<i>Thrombotic factors</i>	? incidence
1. Heritable thrombophilias	
a. Single gene defects factor V Leiden (fVL), MTHFR, factor deficiencies	
b. Antibody-mediated thromboses (APAS, anti-beta2G1)	Most are included among other categories (e.g., immune, genetic)
<i>Other factors</i>	10%
1. Altered uterine receptivity (integrins, adhesion molecules)	
2. Environmental	
a. Toxins	
b. Illicit drugs	
c. Cigarettes and caffeine	

3. Placental abnormalities (circumvallate, marginate)**4. Medical illnesses (cardiac, renal hematologic)****5. Male factors****6. Exercise****7. Dyssynchronous fertilization**

DES, diethylstilbestrol; MTHFR, methylene tetrahydrofolate reductase; APAS, antiphospholipid antibody syndrome.

Neither family history nor a history of prior term births is sufficient to rule out a potential parental chromosomal abnormality. Whereas the frequency of detecting a parental chromosomal abnormality is inversely related to the number of previous spontaneous losses (9), the chance of detecting a parental chromosomal abnormality also is increased among couples that have never experienced a live birth. Abnormalities may also be detected by parental karyotype analysis of couples with a history of spontaneous abortions interspersed with stillbirths and live births (with or without congenital anomalies).

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Unfortunately, the use of parental karyotyping in the evaluation of structural chromosomal causes of RPL may ultimately become insufficient. Evidence now suggests that paternal chromosomal abnormalities may be isolated within particular fertilizing spermatozoa (11), and aneuploid spermatozoa may be particularly motile (12).

Other structural chromosome anomalies, such as inversions and insertions, as well as chromosomal mosaicism and single gene defects, may also contribute to recurrent abortion. X-linked disorders can be linked to recurrent abortion in female offspring but uncommonly result in recurrent abortion of male offspring (13). Single gene defects and their resulting disorders (e.g., the delta f 508 mutation and cystic fibrosis) may be recognized through analysis of detailed family histories or the identification of some pattern of anomalies characteristic of a known heritable syndrome.

Thrombophilias

The role of inherited thrombophilias in RPL has generated a great deal of interest (14,15,16). This heterogeneous group of disorders results in increased venous or arterial thrombosis. Their associations with pregnancy loss rest on both proved (17) and hypothetical alterations in placental growth and development, particularly placental vascular development. Abnormal placental vascularization and inappropriate placental thrombosis would link these thrombophilic states to pregnancy loss. Although some thrombophilic states may be acquired, most are heritable. **Those heritable thrombophilias most often linked with reference to RPL include hyperhomocysteinemia, activated protein C resistance associated with mutations in factor V, deficiencies in proteins C and S, mutations in the prothrombin gene promotor, mutations in prothrombin, and mutations in antithrombin III.**

As with spontaneous pregnancy loss, inherited and combined inherited-acquired thrombophilias also are surprisingly common. More than 15% of Caucasians carry an inherited thrombophilic mutation (15). **The most common of these are factor V Leiden mutations, mutations in the promoter region of the prothrombin gene, and mutations in the gene encoding methylene tetrahydrofolate reductase (MTHFR).** These disorders have been estimated to be present in their heterozygous state in approximately 5%, 2% to 3%, and 11% to 15% of healthy Caucasian populations, based on various studies (16,17,18,19,20). These common mutations are associated with mild

thrombotic risks. It remains unclear whether homozygous *MTHFR* mutations even is associated with vascular disease (21). **In contrast, more severe thrombophilic deficiencies, such as those of antithrombin and protein S, are much less common in the general population.** These epidemiologic data support the hypothesis that a selective genetic advantage may accompany carriage of common heritable thrombophilias. To illustrate this point, women with activated protein C resistance caused by the factor V Leiden mutation have reduced blood loss at delivery (22), and factor V Leiden carriage has been shown to improve pregnancy rates in intracytoplasmic sperm injection/ *in vitro* fertilization, suggesting a positive role in implantation (23). It is important to note that the epidemiology of factor V Leiden mutations is specific to Caucasian populations. Factor V Leiden and prothombin gene mutations are rare in African and Asian populations, despite similar incidences of venous thromboembolism (VTE) in these groups (24,25,26,27). Protein C, protein S, and antithrombin mutations are the most important risk factors for VTE among many Chinese populations (28). These ethnic and geographic differences are important considerations when faced with decisions concerning diagnostic testing in patients with a history of recurrent fetal loss.

Inherited thrombophilic mutations have been estimated to be causative in 50% of VTE during pregnancy (15). Approximately 40% of episodes of venous or arterial thromboembolic phenomena occur in patients carrying a heritable mutation (29). Associations between thrombophilias and adverse fetal outcomes cover a range of early gestational and obstetric disorders. These disorders include isolated and recurrent, early and late spontaneous pregnancy losses, intrauterine growth restriction (IUGR), intrauterine fetal demise

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(IUFD), placental abruption, and pregnancy-induced hypertension (PIH). This discussion will focus on pathophysiologic mechanisms, diagnostic testing, and treatment strategies for patients with RPL who may have an inherited or acquired predisposition to thrombosis (excluding the antiphospholipid syndrome).

The basis for the association between adverse fetal outcomes and heritable thrombophilias has focused on the mechanisms of impaired placental development and function secondary to venous or arterial thrombosis at the maternal–fetal interface. These findings have been noted in the placentas of women with adverse fetal outcomes and known inherited thrombophilias, but have occurred likewise in patients with similar outcomes who lack inherited thrombophilic risk (30,31,32,33,34). Discussions of the role of placental thrombosis in early pregnancy losses (≤ 10 weeks of gestation) have been particularly contentious, citing a series of experiments showing that maternal blood does not flow into the intervillous spaces of the human placenta until approximately 10 weeks of gestation (35,36,37,38). Before establishment of intervillous circulation, however, nutrient transfer from maternal blood to fetal tissues appears to depend on transudation that, in turn, relies on flow through the uterine vasculature. This finding suggests that maternal or fetal thrombotic episodes in the developing placental vasculature could equally be devastating before or after the establishment of intervillous circulation near 10 weeks of gestation. Timing of fetal demise among patients with pregnancy loss, however, does provide diagnostic clues, and its documentation is important in investigations into the causes and treatment of RPL.

Most preclinical and early clinical pregnancy losses are the result of *de novo* fetal aneuploidy (39). This is also thought to be true of anembryonic pregnancy losses. The presence of pregnancy losses resulting from *de novo* fetal aneuploidy, whether early and undocumented or documented through evaluation of chromosomal content in fetal tissues, complicates the results of many published studies. **The presence or absence of fetal aneuploidy must be documented in all investigations of RPL, and their potential as**

a confounding factor should be discussed in any assessment of outcome. The timing of fetal demise and the need for chromosomal analysis of any collected fetal tissue should be carefully weighed when diagnostic and therapeutic investigations into thrombophilia-related causes of RPL are being considered. **Very early pregnancy losses (biochemical, anembryonic) and known aneuploid fetal losses may be less likely to be altered by the presence of an underlying thrombophilic state and can reasonably be dismissed as indications for thrombophilia testing among patients with otherwise unexplained RPL.**

The coagulation system relies on a complex cascade of prothrombotic enzymatic activations (often via serine proteases) in delicate balance with antithrombotic pathways. Although pregnancy is most simply described as prothrombotic, the alterations in the coagulation system associated with pregnancy represent a state of compensated disseminated intravascular coagulation (DIC) (40). Human hemochorial placentation is unique and inherently unstable. Placental development involves invasion into the maternal decidua and its vasculature and requires precise control of hemostasis and fibrinolysis. Delicate control mechanisms exist locally within the placenta (41) and globally within the pregnant woman. Hormonal and related physiologic changes characteristic of pregnancy affect important components of the clotting cascade, the fibrinolytic cascade, and platelet physiology.

Clot formation can be initiated through two pathways, called the extrinsic and intrinsic clotting cascades (Fig. 31.1). Both respond to blood vessel damage and the release of tissue factor (TF). Tissue factor is a glycoprotein expressed on the surface of cells surrounding blood vessels. It is not expressed on the endothelium of the blood vessel itself, so exposure of blood to TF is a sensitive indicator of vascular damage. The extrinsic clotting cascade begins with the interaction of newly released TF with factor VII of

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the clotting cascade. The complex formed by TF and factor VII can either directly activate factor X or activate factor X via the intrinsic pathway. In the intrinsic pathway, the TF/factor VII complex activates factor IX to factor IXa (activated factor IX). Factor IXa then complexes with factor VIIIa. In combination, factors IXa and VIIIa activate factor X. Activation of factor XII after binding to negatively charged surfaces also can initiate the intrinsic pathway. Via this route, activated factor XII cleaves factor XI, generating factor XIa. Factor XIa can act as an alternate activator of factor IX. Extrinsic and intrinsic clotting cascades converge in the activation of factor X to factor Xa. Activated factor X (Xa) catalyzes the conversion of prothrombin (factor II) to thrombin (factor IIa). The presence of activated factor V, factor Va, is required for this conversion. Thrombin, in turn, converts fibrinogen to fibrin, an essential building block for stable clot formation. Thrombin also activates factor XIII, which in turn cross-links fibrin monomers and thereby stabilizes the fibrin clot.

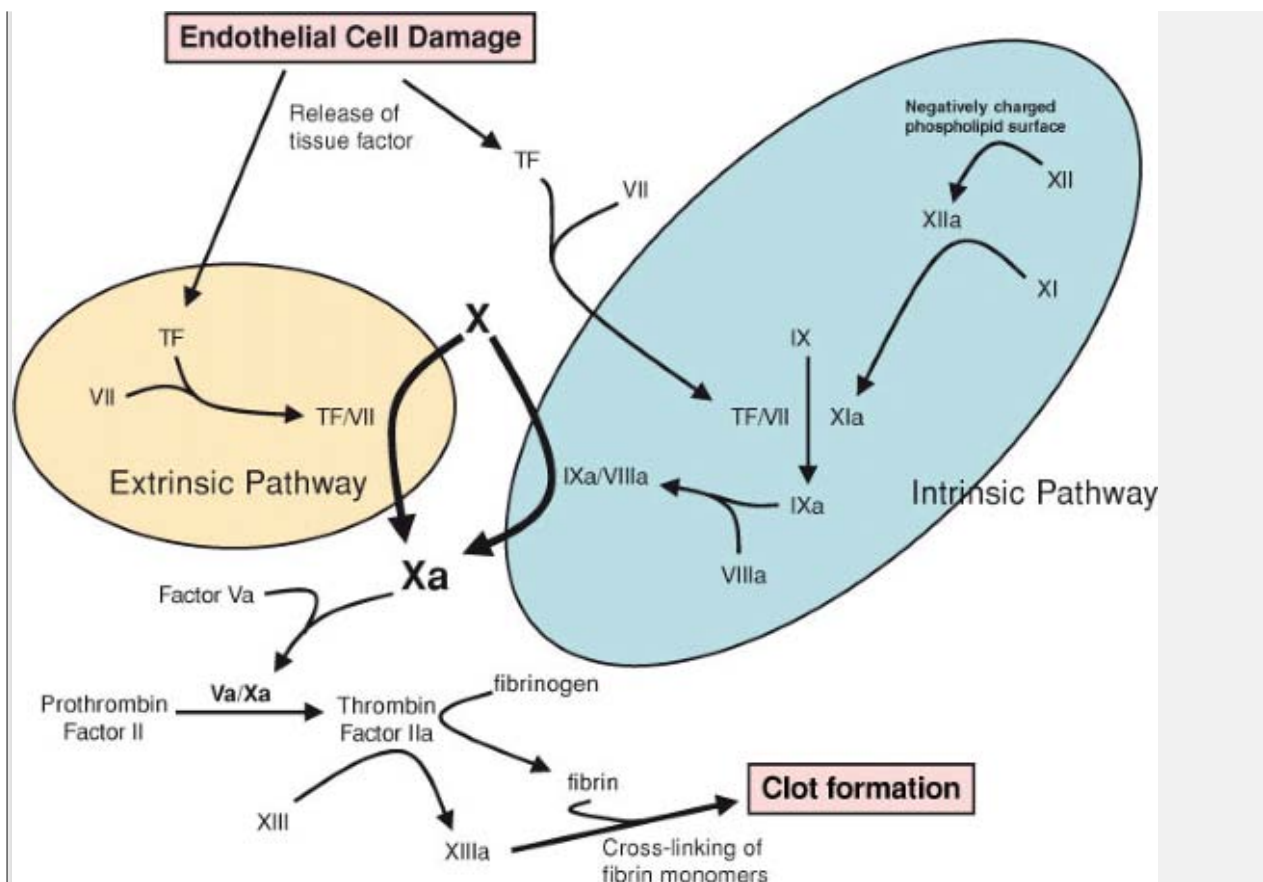


Figure 31.1 The clotting cascade. Physiologic clotting is initiated by endothelial cell damage or abnormal exposure of negatively charged phospholipids to serum and blood components. Procoagulant pathways in black are part of the clotting cascade and are prothrombotic. Both lead to activation of cascades of proteolytic enzymes and cleavage of clotting factors. The extrinsic and intrinsic pathways are initiated by distinct mechanisms. They merge at the activation of factor X to form the common pathway. For all coagulation factors, the subscript *a* denotes the activated form of the factor.

To avoid uncontrolled thrombosis in response to tissue damage or alternate activation of the coagulation cascade, a number of antithrombotic control mechanisms are activated in conjunction with clot formation (Fig. 31.2). Important to this discussion are those mechanisms involving antithrombin (formerly antithrombin III), protein C, and protein S. Proteins C and S are vitamin K-dependent factors that are activated on clot formation. Activation is initiated by complexes of thrombomodulin and thrombin at sites of endothelial damage. Complexes of activated protein C and S inactivate factors Va and VIIIa, thereby inhibiting their associated procoagulant activities. Antithrombin is a serine

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protease inhibitor that binds irreversibly to serine proteases. Proteases that bind antithrombin include factors IXa, Xa, XIa, and XIIa. Antithrombin also accelerates dissociation of factor VIIa tissue factor complexes, thereby inhibiting intrinsic and extrinsic clotting pathways at their points of initiation. Finally, as its name suggests, antithrombin binds to and inhibits thrombin (factor IIa). Fibrinolysis also acts to delimit uncontrolled coagulation (see Fig. 31.2). Mechanisms for fibrinolysis include cleavage of the fibrin clot by plasmin and the formation of fibrin degradation products (FDPs or FSPs). Plasmin activity is, in turn, controlled by plasminogen activator inhibitors (e.g., PAI-1).

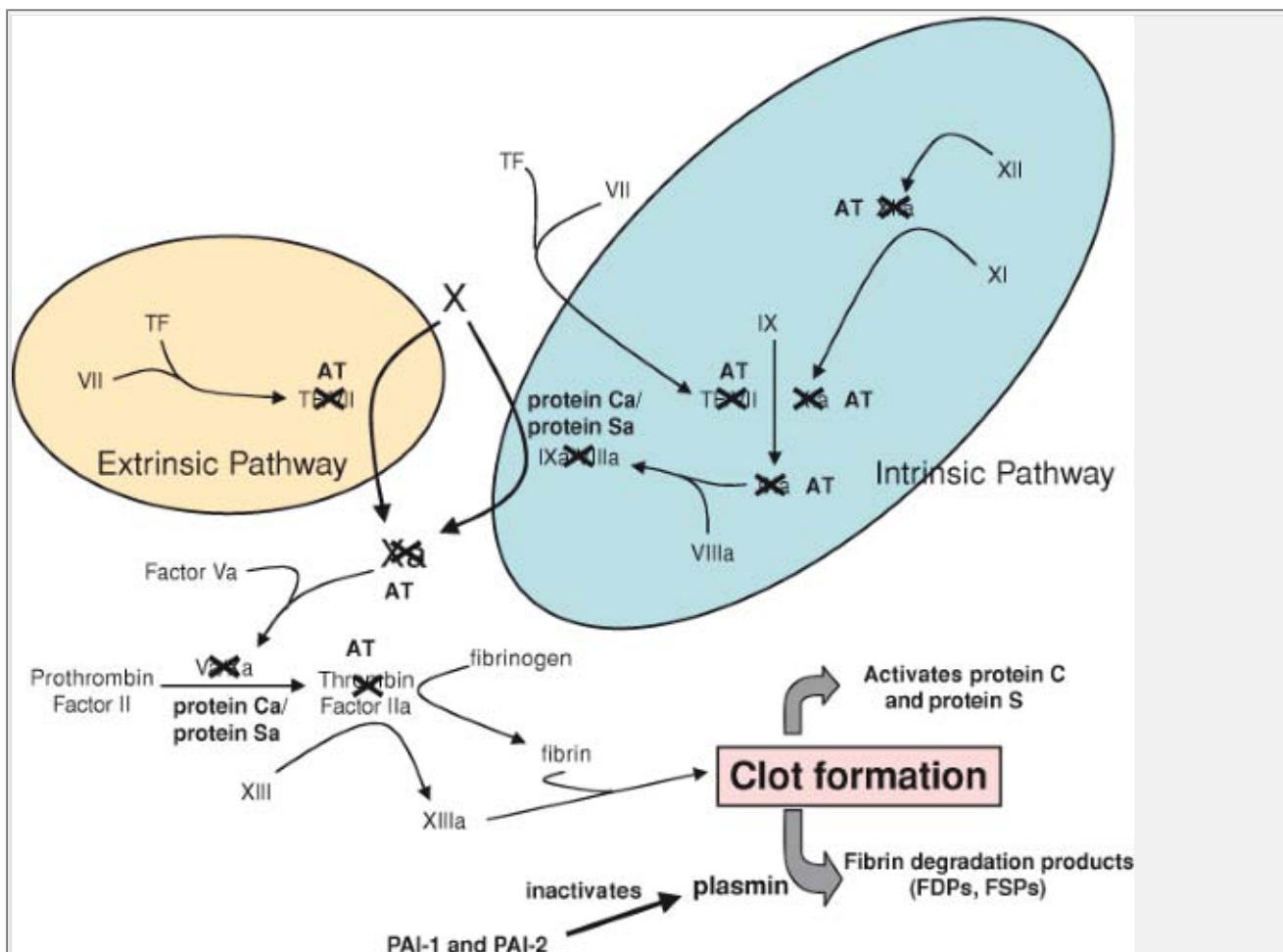


Figure 31.2 Physiologic mechanisms that counteract the clotting cascade. The procoagulant cascade is inhibited by several physiologic mechanisms. The balance between pro- and antithrombotic pathways determines the state of coagulability. Antithrombotic mechanisms include the action of antithrombin (AT) and of proteins C and S. The sites of inhibition by these substances are depicted by an X. Plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) indirectly inactivate plasmin. Plasmin plays an important role in the dissolution of coagulated blood. For all coagulation factors, the subscript *a* denotes the activated form of the factor. FSP, fibrin split products; FDP, fibrin degradation products.

Prothrombotic changes associated with pregnancy include increases in the amounts or the activities of factors in the clotting cascade and decreases in those counteracting clotting. The former includes pregnancy-associated elevations in factors VII, VIII, X, XII, von Willebrand's factor, and fibrinogen levels (40,42,43). All of these factors increase throughout gestation. Factor II, factor V, and factor XIII levels also increase early in pregnancy but return to normal levels after the first trimester (40,44). Normal pregnancy has been associated with the development of activated protein C resistance (acquired APCR)

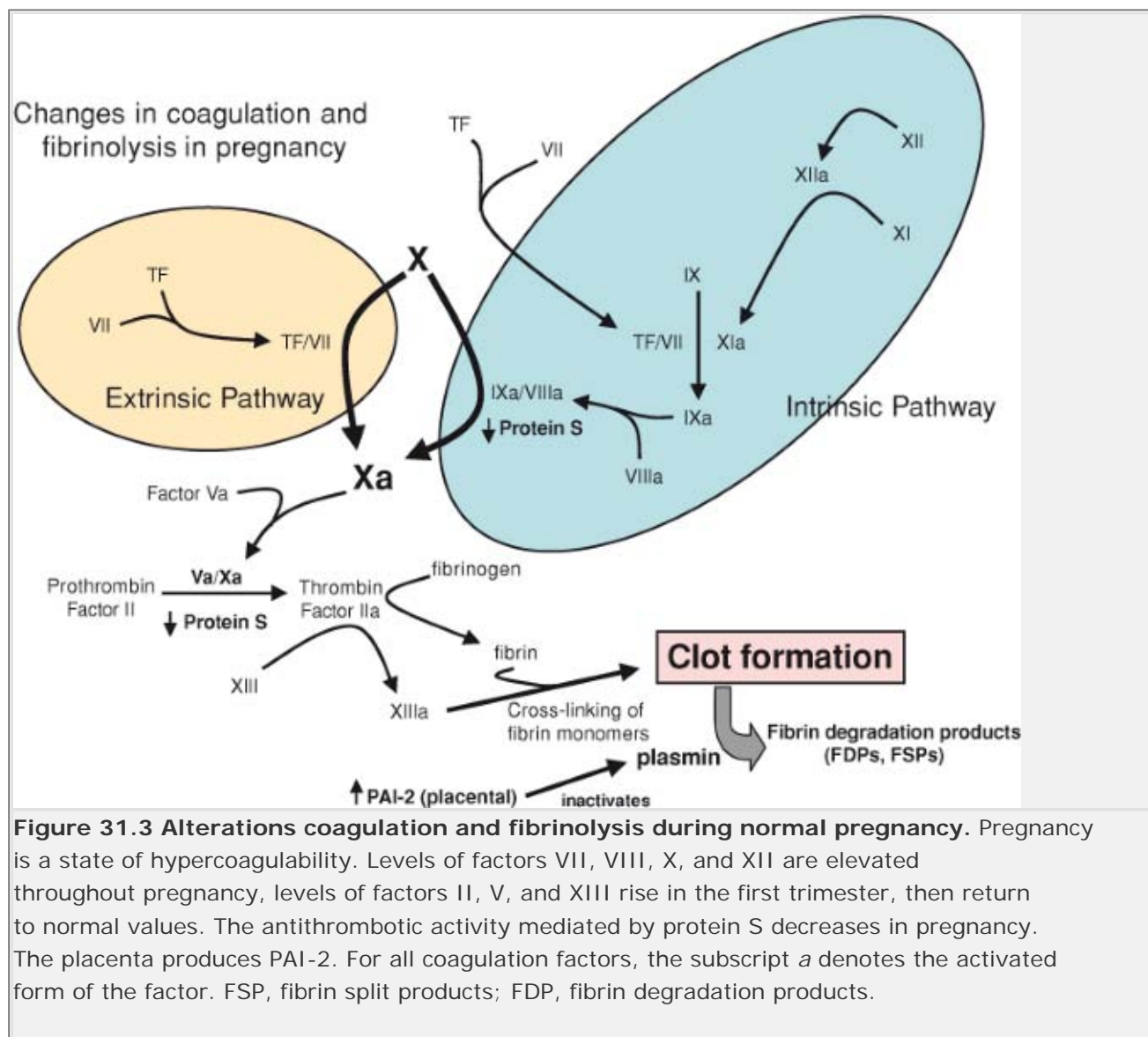
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via mechanisms that remain unclear (45). Changes in balancing antithrombotic control mechanisms during pregnancy also favor clot formation. Whereas the activities of protein C and antithrombin remain fairly constant during the course of pregnancy, those of protein S decrease significantly. Protein S activity decreases in conjunction with pregnancy-induced increases in the production of C4b-binding protein, a complement factor-binding protein that forms a complex with protein S, making it unavailable for interaction with activated protein C (46). This increased binding, however, does not fully explain the level of decrease in protein S activity during pregnancy (46).

Fibrinolysis is impaired during pregnancy, with decreases in fibrinolytic activity beginning at approximately 11 to 15 weeks of gestation (40). A significant factor in this impairment is a marked decrease in plasmin activity resulting from placental production of the plasmin-inhibitor, PAI-2 (47,48). In conjunction with these changes, however, FDP levels rise in pregnancy, beginning at approximately 20 weeks of gestation and continuing their rise throughout pregnancy (40,48). In normal pregnancy, platelet function and turnover is unchanged (Fig. 31.3). In the third trimester, platelet number typically decreases, the result of increased platelet consumption. This benign gestational thrombocytopenia can reach levels less than $80 \times 10^9/L$ (49). Collectively, pregnancy-associated alterations in the amounts and activities of prothrombotic clotting factors, anticoagulant control mechanisms, and fibrinolysis support the determination of human pregnancy as a state of

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compensated DIC. Although these changes reverse during the 4 to 6 weeks following delivery (40,49), **the vascular damage associated with delivery is an additional significant risk factor for thrombosis, making the immediate postpartum period an important continuation of the prothrombotic state associated with pregnancy.**



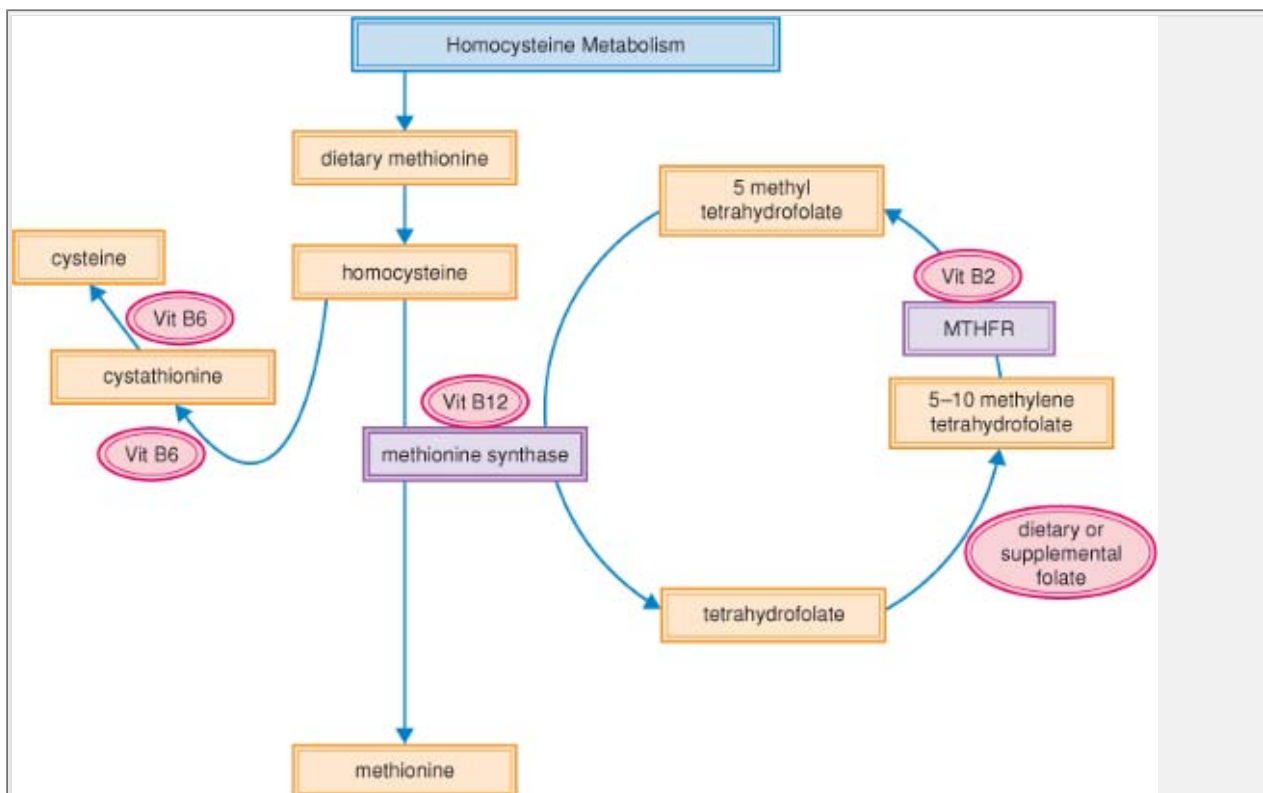


Figure 31.4 Homocysteine metabolism. Dietary methionine is metabolized either to cysteine or back into methionine. Homocysteine, a prothrombotic metabolite, is an intermediate in this process. Conversion of homocysteine to methionine requires transfer of a methyl group from 5 methyl tetrahydrofolate. The conversion of folate to 5 methyl tetrahydrofolate is a multistep process requiring vitamin B₂ as a cofactor for the enzyme, methylene tetrahydrofolate reductase (MTHFR). Vitamin (Vit) B₁₂ is a required cofactor for the enzyme methionine synthase. Vitamin B₆ is also required for metabolism of sulfur-containing amino acids, such as methionine.

Circulating homocysteine is derived from dietary methionine. Homocysteine, in turn, is metabolized either into cystathionine or back into methionine (Fig. 31.4). The latter process involves the enzyme methionine synthase. Methionine synthase requires donation of a methyl group from 5 methyl tetrahydrofolate to produce methionine, and the enzyme *methylene tetrahydrofolate reductase (MTHFR)* is involved in the production of 5 methyl tetrahydrofolate from dietary folate sources (14). The nutritional supplements folic acid, vitamins B₂, B₆, and B₁₂ are all required for proper metabolism of homocysteine; therefore, their deficiency is associated with acquired elevations in circulating homocysteine levels (15,18,50). Although heritable deficiencies in the enzymes required for metabolism of homocysteine have been described for the pathways leading to cystathionine formation and those involved in reconversion to methionine (14,50,51,52). Point mutations in *MTHFR* are surprisingly common (16,19), and can be associated with hyperhomocysteinemia and thrombosis (50,51,52).

Those heritable thrombophilias most often linked to RPL include hyperhomocysteinemia, activated protein C resistance associated with mutations in factor V, deficiencies

in proteins C and S, and mutations in the prothrombin promoter and antithrombin. These inherited disorders are mainly autosomal dominant and display a wide variation in prevalence and in the severity of morbidity associated with gene carriage. The latter

two characteristics have direct reciprocal correlations in the Caucasian population. **Consistent with general thrombotic risk, carriage of combinations of two or more inherited thrombophilic defects has particularly strong association with adverse pregnancy outcomes** (16,19,53). Acquired thrombophilias associated with RPL include hyperhomocysteinemia and activated protein C resistance. Most of the data linking thrombophilic states to recurrent fetal loss consist of small- to moderate-sized prevalence studies (53,54,55,56,57,58,59,60,61). Recent attempts to pool these data into meta-analyses have allowed more informed recommendations on the testing of patients presenting with RPL (62,63,64). Collectively, these studies suggest that testing for the factor V Leiden mutation, protein S levels, prothrombin promoter mutations, homocysteine levels, and global activated protein C resistance is of use in Caucasian patients with a history of repetitive first- or second-trimester losses. These recommendations do not necessarily apply to non-Caucasian patients. Individual studies directly linking hyperhomocysteinemia, folic acid, vitamin B₁₂, and *MTHFR* mutations to RPL have been contradictory (30,31,51,52,53,54,55,56). Recent studies that have evaluated pooled data from previous investigations (one via meta-analysis) show these conditions to be linked to risk of RPL (62).

With the recent completion of the human genome project and the rapid development of novel and improved molecular cytogenetic techniques (65), many advances and additional insights into the contribution of parental genetic abnormalities to RPL can be anticipated.

Anatomic Abnormalities

Anatomic abnormalities of the both the uterine cervix and the uterine body have been associated with RPL. These anatomic causes may be either congenital or acquired. During development, the uterus forms via the apposition of a portion of bilateral hollow tubes called the müllerian ducts. The dissolution of the walls of these ducts along their site of apposition allows formation of the intrauterine cavity, the intracervical canal, and the upper vagina. Congenital uterine anomalies may, therefore, include incomplete müllerian duct fusion, incomplete septum resorption, and uterine cervical anomalies. Although the causes underlying many of the congenital anomalies of the female reproductive tract are unclear, it has been well documented that prenatal exposure to maternally ingested diethylstilbestrol (DES) results in complex congenital uterine, cervical, and vaginal changes.

Historically, all congenital reproductive tract abnormalities have been linked to both isolated spontaneous pregnancy loss and to RPL (66), although the presence of an intrauterine septum and prenatal exposure to DES demonstrate the strongest associations (67,68). In fact, women with an intrauterine septum may have as high as a 60% risk for spontaneous abortion (69). Uterine septum-related losses most frequently occur during the second trimester. However, if an embryo implants into the poorly developed endometrium overlying the uterine septum, abnormal placentation and resultant first-trimester losses may occur as well (70). The most common uterine congenital anomaly associated with *in utero* DES exposure is hypoplasia, which may contribute to first- or second-trimester spontaneous abortions, incompetent cervix, and premature labor (71,72). Congenital anomalies of the uterine arteries also may contribute to pregnancy loss via adverse alterations in blood flow to the implanted blastocyst and developing placenta (73).

Acquired anatomic anomalies have likewise been linked to both isolated and RPL. These abnormalities include such disparate conditions as intrauterine adhesions, uterine fibroids, and endometriosis. Endometrium that develops over an intrauterine synechiae or over a fibroid that impinges in the intrauterine cavity (submucous) may be inadequately vascularized (74). This may promote abnormal placentation for any embryo

attempting to implant over such lesions. Although data supporting these concepts are a bit tenuous, this abnormal placentation may lead to spontaneous pregnancy loss. Less clear is the association between intramural fibroids and RPL, but it is suggested that large (greater than 5 cm) intramural fibroids are associated with pregnancy loss and that removal improves outcomes (67,75).

Endocrine Abnormalities

The endocrinology of normal pregnancy is complex. **Because spontaneous pregnancy is critically dependent on appropriately timed endocrinologic changes of the menstrual cycle, it is not surprising that those endocrine abnormalities that ultimately alter pregnancy maintenance may mediate their effects during the follicular phase of the cycle in which conception occurs, or even earlier.** Modifications in follicular development and ovulation, in turn, may be reflected in abnormalities of blastocyst transport and development, alterations in uterine receptivity to the implanting blastocyst, and improper functioning of the corpus luteum. **Beginning with ovulation and lasting until approximately 7 to 9 weeks of gestation, maintenance of early pregnancy depends on the production of progesterone by the corpus luteum. Normal pregnancies are characterized by a luteal-placental shift at about 7 to 9 weeks of gestation, during which the developing placental trophoblast cells take over progesterone production and pregnancy maintenance (76). Spontaneous pregnancy losses occurring before 10 weeks of gestation may result from a number of alterations in normal progesterone production or utilization. These include failure of the corpus luteum to produce sufficient quantities of progesterone, impaired delivery of progesterone to the uterus, or inappropriate utilization of progesterone by the uterine decidua.** Pregnancy failures may also occur near the time of the expected luteal-placental shift if the trophoblast is unable to produce biologically active progesterone following demise of the corpus luteum.

Endocrinologic factors associated with recurrent abortion include luteal phase insufficiency, diabetes mellitus, hypersecretion of luteinizing hormone (LH), thyroid disease, and potentially insulin resistance and the polycystic ovarian syndrome (PCOS), hyperprolactinemia, and decreased ovarian reserve. Luteal phase insufficiency or luteal phase defects (LPD) are characterized by inadequate luteal milestones. They most likely relate to adverse pregnancy outcome via inadequate or improperly timed endometrial development at potential implantation sites. Luteal phase defect has many causes, some of which are associated with hypersecretion of LH. Although the mechanism underlying the association of elevated LH levels with RPL remains incompletely understood, abnormal LH secretion may have direct effects on the developing oocyte (premature aging), on the endometrium (dyssynchronous maturation), or both. Many patients with elevated LH levels also display physical, endocrinologic, and metabolic characteristics of PCOS. In fact, **some studies report ovarian radiologic evidence of PCOS in as many as 40% to 80% of patients experiencing RPL (77,78).** In addition to inappropriately elevated LH levels, PCOS patients are frequently obese and often have elevated circulating androgen levels. Although not undisputed (78), both changes have been linked to RPL (77,79), and elevated androgen levels have been shown to adversely affect markers of uterine receptivity in women with a history of RPL (80).

Many women with PCOS have metabolic alterations in glycemic control characterized by insulin resistance (see Chapter 29). This too may be directly or indirectly related to adverse pregnancy outcome, and it may be linked to the mechanisms for spontaneous pregnancy loss among women with type 2 diabetes mellitus (81). Women with overt type 2

diabetes mellitus appear to exhibit a threshold of pregestational glycemic control above which spontaneous pregnancy loss is increased (82,83). In fact, hyperglycemia has now been linked directly to embryonic damage (84). In cases of advanced type 2 diabetes with accompanying vascular complications, subsequent pregnancy loss may result from compromised blood flow to the uterus.

Patients with thyroid disease often have concomitant reproductive abnormalities, including ovulatory dysfunction and LPD. In addition, the metabolic demands of early pregnancy mandate increased levels of thyroid hormones. It is, therefore, not surprising that hypothyroidism has been associated with spontaneous pregnancy loss and with RPL (85). Whether clinically euthyroid patients with antithyroid antibodies have higher rates of RPL continues to be debated (86,87,88,89). The mechanism for an association remains unclear; however, these antibodies may be markers of more generalized autoimmunity or may predict an impaired ability of the thyroid gland to respond to the demands of pregnancy.

Two additional endocrinologic abnormalities have been linked with RPL, although data to support these associations are lacking. **Animal models suggest that elevated prolactin levels may adversely affect the function of the corpus luteum; however, this concept is not well supported in humans (90,91).** Some have suggested that elevated prolactin levels may promote pregnancy wastage via direct effects on the endometrium or indirect immunomodulatory mechanisms (92). Most recently, attempts have been made to correlate markers of ovarian reserve (day 3 follicle-stimulating hormone and day 3 estradiol response to the *clomiphene* challenge test) with RPL (78,93,94). At present, no consensus exists concerning this potential association.

Maternal Infection

Infection of the reproductive tract with bacterial, viral, parasitic, zoonotic, and fungal organisms has been linked theoretically to pregnancy loss. The most extensively studied pathogens are mycoplasma, ureaplasma, *Chlamydia trachomatis*, and β -streptococcus (95,96), and recent data have focused on the roles of some of these proposed organisms in RPL. One prospective comparison trial involving 70 patients with RPL reported no elevations in any markers for present or past infection with *C. trachomatis* when compared with controls (97). In contrast, a very large, prospective trial has demonstrated a link between the detection of bacterial vaginosis and history of second-trimester pregnancy loss among 500 patients with RPL (98). In this study, the likelihood of detecting bacterial vaginosis positively correlated with cigarette smoking.

The mechanism linking specific organisms to either isolated or RPL remains unclear and must certainly differ among infectious organisms. Certain viral organisms, such as herpes simplex virus (HSV) (99) and human cytomegalovirus (CMV) (100) can directly infect the placenta and fetus. The resulting villitis and related tissue destruction may disrupt pregnancy. Another theoretic possibility is that infection-associated early pregnancy loss may result from immunologic activation that occurs in response to pathologic organisms. A large body of evidence supports the role of this mechanism in adverse events that occur later in gestation, such as intrauterine growth restriction (101), premature rupture of membranes, and preterm birth (102). Alternatively, mechanisms that protect the fetus from autoimmune rejection also may protect virally infected placental cells from recognition and clearance. This could potentially promote periods of unfettered infectious growth for some of the pathogenic organisms gaining entry to the reproductive tract (103).

Immunologic Phenomena

Although there has been extensive information published on the immunologic aspects of RPL, there is a lack of consensus as to the mechanisms and the impact of therapeutic intervention. The detection of a therapeutic effect is difficult, and studies are complicated by the fact that many patients with RPL seek care after the pregnancy is lost but before the fetus or embryo is expelled. In these cases, the physiologic immune reaction to the presence of nonviable tissue may mask any alternative, underlying immune causes for the demise itself. Finally, it is very likely that there is a wide variety of immune

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alterations that may cause isolated or RPL. At least ten well-supported immune mechanisms, each potentially important in pregnancy maintenance, have been identified (104).

Before launching into the most commonly accepted causes of immune-mediated pregnancy loss, a brief review of some of the important concepts in basic immunology is warranted for reference. These descriptions are presented in general terms here and further defined in Chapter 6.

Immune responses classically are divided into *innate* and *acquired* responses. *Innate responses* represent the body's first line of defense against pathogenic invasion. They are rapid and are not antigen specific. Cell types and mechanisms typically considered vital to innate immunity include complement activation, phagocytosis by macrophage, and lysis by natural killer (NK) and natural killer T (NKT) cells and possibly by TCR $\gamma\delta$ ⁺ T cells. *Acquired immune responses*, in contrast, are antigen specific and are largely mediated by T cells and B cells. Acquired responses can be further classified as *primary* (response associated with initial antigen contact) and *secondary* (rapid and powerful anamnestic responses associated with subsequent contact to the same antigen).

Antigen specificity is generally regulated by two sets of genes in the major histocompatibility complex (MHC), located on chromosome 6 in humans. MHC class I molecules (HLA-A, -B, and -C) are present on the surface of nearly every cell in the human body and are important in defense against oncogenic transformation and intracellular pathogens, such as viral infection. Class I MHC molecules act as important ligands for both the T-cell receptor on CD8⁺ cytotoxic/suppressor T cells and for a variety of receptors on NK cells (105). Class II MHC molecules (HLA-DR, HLA-DP, and HLA-DQ), in contrast, are present on the surface of a limited number of antigen-presenting cells, including dendritic cells, macrophage and monocytes, B cells, and tissue-specific cells such as the Langerhans cells in the skin. These molecules are important in defense against extracellular pathogens, such as bacterial invaders. The major ligand for MHC class II is the T-cell receptor on CD4⁺ T helper cells.

One very important concept in immunology that has particular application to pregnancy is that of immune tolerance. It has been well described that bone marrow-derived T cells pass through the fetal thymus during early development. During this developmental interval, the T cells encounter a process termed *thymic education*. During thymic education, T cells are chosen that express either the CD4 or the CD8 co-receptor, and autoreactive cells are effectively eliminated. In short, this education promotes T-cell tolerance, allowing selection and survival only of those T cells that can recognize nonself but will not react against self.

Recently, a subpopulation of CD4⁺ T cells has been described that strongly express CD25 on their cell surface. These CD4, CD25⁺ cells are called regulatory T lymphocytes (T reg cells) (106). T reg cells, when activated by autoantigens, can suppress activated inflammatory cells. They may have particular importance in avoidance of tissue destruction associated with inflammation, possibly with applications to tolerance.

These immunologic characteristics have been most thoroughly described and investigated for the immune effector cells populating the peripheral immune system. The peripheral immune system consists of the spleen and peripheral blood, and it is generally responsible for protection against blood-borne pathogens. Pathogens that enter the host via the extensive surface areas of the lacrimal ducts, respiratory system, gastrointestinal tract, mammary ducts, and genitourinary tract encounter a very distinct and important immune environment—that of the mucosal immune system. Although the mucosal immune system may be responsible primarily for the initial protection against most exogenous pathogens, knowledge of its immune characteristics lags far behind that of the peripheral immune

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system. Insight into the specific characteristics of immunity within the reproductive tract is even further limited.

Cellular Immune Mechanisms

Many of the immune theories surrounding the causes of isolated and recurrent spontaneous pregnancy losses have stemmed from attempts to define immunologic rules as they apply specifically to the mucosal reproductive tract. Four main questions summarize much of the theoretical thinking surrounding pregnancy maintenance and reproductive immunology:

- Which immune cells populate the reproductive tract, particularly at implantation sites?
- How do these cells arrive at this mucosal immune site, and are they educated in the same way as those populating the periphery?
- How do the characteristics of antigen presentation differ at the maternal–fetal interface?
- What regulatory mechanisms specifically affect reproductive tract immune cells?

Resident Cells

Immune cells populating the reproductive tract exhibit many characteristics that distinguish them from their peripheral counterparts. In particular, the human endometrium is populated by T cells, macrophage, and NK-like cells, but very few B cells (107,108). The relative proportions of these resident cells vary with the menstrual cycle and change dramatically during early pregnancy. In fact, **around the time of implantation, one particular cell type comprises between 70% and 80% of the total endometrial lymphocyte populations** (107,108). This cell type is called a variety of names, including *decidual granular lymphocytes (DGL)*, *large granular lymphocytes (LGL)*, and *decidual NK cells*. This heterogeneity of names reflects the fact that this particular cell type differs from similar cells isolated from the periphery, although most believe it to be an NK cell variant. If these cells are considered NK, the implantation site represents the largest accumulation of NK cells in any state of human health or disease. The true function of these cells remains unclear, but their remarkable abundance at the maternal–fetal interface is compelling (109,110). Other immune cells that have been described in the periphery have characteristics of both NK cells and of T cells. These NKT cells have recently been shown to play a role in pregnancy loss in animal models (111). They are present in the decidua in

humans and may play an important immunoregulatory role at this site (112).

In the peripheral immune compartment, most T cells express a T-cell receptor made up of an $\alpha\beta$ heterodimer (TCR $\alpha\beta^+$). In addition to TCR $\alpha\beta^+$ T cells, the human reproductive tract also is populated by a subset of T cells with a distinctive T cell receptor composed of the $\gamma\delta$ heterodimer (TCR $\gamma\delta^+$), and the numbers of these cells increases in early pregnancy (113,114,115). TCR $\gamma\delta^+$ T cells appear to fulfill functions quite distinct from their $\alpha\beta^+$ counterparts; these functions may include direct, non-MHC-restricted recognition of antigens within tissues (116). In fact, TCR $\gamma\delta^+$ T cells may fill a protective niche missed or poorly covered by B cells and TCR $\alpha\beta^+$ T cells. The role and importance of TCR $\gamma\delta^+$ cells in the reproductive tract and, more particularly, in pregnancy maintenance deserves further attention.

Finally, it has been suggested that **a subset of macrophage, termed "suppressor" macrophage, may be implicated in pregnancy maintenance**. These specific cells differ from typical macrophage in their promotion of anti-inflammatory effects, and they have been detected in normal murine placenta (117). Their presence in human decidual specimens requires further investigation. T reg cells are also of the "suppressor" functional phenotype. In pregnant mice and women, these specialized CD4⁺ cells are systemically

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expanded in an alloantigen independent fashion (118) and can suppress adverse maternal responses to self (119) and to the fetus (120).

The human decidua is populated by characteristic immune effector cells. Investigations into whether alterations in these cells (including T cells, decidual NK cells, and NKT cells) determine pregnancy outcome have been hampered by insufficient patient numbers to allow meaningful conclusions. These immune cell populations have been reported to be altered in patients with RPL (121,122,123) but not in patients experiencing isolated spontaneous pregnancy losses (115).

Immune Cell Education and Homing to the Reproductive Tract

The implanting fetus represents the most common model of allograft acceptance. The ability of the maternal immune system to avoid rejection of the implanting fetus in an uncomplicated pregnancy is a manifestation of immune tolerance. This observation raises questions about how the resident decidual immune effector cells are selected and educated, how they are recruited to reproductive sites, and how they are maintained once they reach this destination. Animal studies have suggested that the rules for selection and maintenance of these cells, in terms of their requirement for MHC and their education within the thymus, may be distinct from those governing either peripheral immune cells or cells within other mucosal sites, including the intestine (124). The immunophenotypes of immune cells populating the human reproductive tract are distinct from both the periphery and from other mucosal sites (125,126). The education of TCR $\gamma\delta^+$ cells populating epithelial sites may occur outside the thymus and might involve mechanisms that substitute for or modify interaction with MHC (115,127). The development of MHC specificity among NK cells is undergoing careful dissection in animal models (128,129) with the hope that these investigations will shed light on similar processes in humans and, specifically, on the selection and maintenance characteristics of decidual NK cells.

It is now becoming increasingly evident that the cells populating mucosal immune tissues select these sites through interactions between cell surface molecules on the immune cell (*integrins*) and cell surface molecules on the endothelial cells of blood vessels within the mucosal tissues (e.g., *selectins*, *VCAM*, *MECA*). This

cellular recruitment process, called homing, has been most thoroughly described for the intestine (130,131). However, both murine (130,132) and human (133) reproductive tract tissues express these integrin/vascular ligand pairs, and the extension of these findings to pregnancy maintenance will surely prove fruitful. Understanding the mechanisms of selection, education, and maintenance of reproductive tract immune effector cells in the normal state is of paramount importance to determining the effects of alterations on disorders and their treatment.

Antigen Presentation at the Maternal-Fetal Interface

Historically, it was proposed that one method by which the implanting trophoblastic allograft could potentially avoid immune detection by the maternal host would be by making itself antigenically invisible. It could downregulate its expression of the MHC-encoded transplantation antigens (some of which would be of paternal origin) and thereby avoid recognition as nonself. Although current knowledge of immunology now makes this theory somewhat obsolete (134), the implanting fetus does, in fact, use this strategy to some extent. It is certainly true that placental trophoblast cells do not express MHC class II molecules (135,136).

Unlike nearly every other cell in the human body, trophoblast cells do not express the classical MHC class I transplantation antigens HLA-A and -B. Rather, a subpopulation of placental cells, specifically the extravillous cytotrophoblast cells, express the classical MHC class I HLA-C products and the nonclassical HLA-E and -G products (103,137,138,139,140,141). These extravillous cytotrophoblast cells are of particular interest because they are characterized by remarkable invasive potential (142,143). These cells move from the tips of the anchoring villae of the human placenta and invade deeply into the maternal

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decidua. They can even replace cells within the walls of decidual arterial vessels (142,143,144). Although the invasive characteristics of extravillous cytotrophoblast may reflect non-MHC-related mechanisms, including well-described integrin switching (145), the intimate contact of these fetal-derived cells with maternal immune effector cells exposes the fetus to recognition as nonself.

It is not known why all placental cells downregulate expression of HLA-A and -B, whereas invasive extravillous cytotrophoblast express HLA-C, -E, and -G. Because NK cells of the innate immune system recognize and kill cells that express no MHC (134), the complete downregulation of MHC would cause trophoblast cells to act as targets for those NK cells that are pervasive at sites of implantation. In addition to possible protection from direct NK cell-mediated killing, the expression of HLA-C, -E, and -G by trophoblast cells may serve a variety of alternative roles. Natural killer cell receptor-mediated interactions with extravillous cytotrophoblast MHC could modulate cytokine expression profiles at the maternal-fetal interface (109,110). **Major histocompatibility complex expression may aid in decidual and vascular invasion by the trophoblast, an activity essential for proper placental development** (146). Whereas definitive correlations between placental MHC class I expression patterns and RPL have yet to be reported, trophoblast expression of HLA-G has been linked to other disorders of placental invasion, such as preeclampsia (146,147). Genetic mutations at the HLA-G locus have also been linked to RPL in some but not all studies (148,149,150,151). Finally, soluble or secreted trophoblast MHC products may aid in the development of maternal immune tolerance to the placenta (152).

Aberrant expression of class II MHC determinants, or enhanced expression of MHC class I on syncytiotrophoblast occurring in response to IFN- γ (153), could mediate abortion by enhancing cytotoxic T-cell attack (154). This theory appears unlikely, however, because

the expression of classical MHC antigens does not seem to be induced on aborted tissues from women experiencing one or more pregnancy losses (155). Finally, MHC class II genotypes appear to affect susceptibility to a variety of diseases, including diabetes and other autoimmune diseases. **A similar link between MHC class II typing and adverse pregnancy outcome has been reported for RPL (156).**

Regulation of Decidual Immune Cells

The characteristics of the interactions between decidual immune effector cells and the implanting fetus may be determined by factors other than those already mentioned. Local regulation of the cells that populate the human decidua will further modify the effects of selection, maintenance, and homing, as well as the distinctive characteristics of antigen presentation at the maternal–fetal interface. These regulatory effects are often targets of investigative efforts because they may offer more direct insight into potential therapies for immune-mediated disorders of pregnancy maintenance. **Three such regulatory mechanisms include (i) alterations in T-helper cell phenotypes, (ii) reproductive hormones and immunosuppression, and (iii) tryptophan metabolism.**

Antigen-stimulated immune responses involving CD4⁺ T cells can be divided into two major classes: T helper 1 (TH1) responses and T helper 2 (TH2) responses.

This subclassification may be overly simple, but it has been useful in broadly defining types of immune responses based on the characteristics of the CD4⁺ cells present, as well as their associated cytokines. The production of these responses rests on the environment in which relatively undifferentiated CD4⁺ TH0 cells become differentiated. Thus, TH0 cells exposed to IFN- γ become TH1-type cells, and those exposed to interleukin IL-1,-4 become TH2-type cells (157). Responses from TH1 cells are associated with inflammation and primarily involve interferon (IFN)- γ and IL-2, and tumor necrosis factor (TNF)- β . Responses from TH2 cells are associated with antibody production and the cytokines IL-10, IL-4, IL-5, and IL-6 (157,158,159). Although TNF- α can be secreted by both TH1 and TH2 cells, it is most often characteristic of a TH1 response (160,161). **A reciprocal regulating relationship exists between TH1 and TH2 cells and cytokines**

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(162,163,164), with one response supporting its own persistence while averting conversion to the other.

Extending these immune regulatory phenomena to pregnancy, the type of CD4⁺ cellular response to the implanting fetus is controlled not only by the types of cells (e.g., T helper cells) in the decidua, but also by the cytokine environment at the maternal–fetal interface. As mentioned previously, the human endometrium and decidua are replete with immune and inflammatory cells capable of cytokine secretion (165,166,167). Cytokines may affect reproductive events either directly or indirectly, depending on the specific cytokines secreted, their concentrations, and the differentiation stage of potential reproductive target tissues. It is now well documented that TH1-type cytokines can be harmful to an implanting embryo (168,169). **Furthermore, most agree that some patients with RPL exhibit a dysregulation of their T helper cellular immune response to antigens at the site of implantation, with typical shifts toward TH1 inflammatory responses (170,171).** Depending on the individual series, 60% to 80% of nonpregnant women with a history of otherwise unexplained recurrent spontaneous abortion have been found to have evidence of abnormal *in vitro* TH1 **cellular immune responses**. Fewer than 3% of women with normal reproductive histories demonstrate these responses (171,172). Rather, most women with normal pregnancies have a TH2 immune response to trophoblast antigens (171).

Methods for the documentation of cytokine dysregulation among patients with RPL also vary

among investigators; some groups have confirmed this abnormality within the endometrium (173,174,175) or among immune cells isolated from the decidua (176) of these patients. Others use peripheral blood lymphocytes (PBL) from women with a history of RPL and stimulate them *in vitro* with trophoblast antigens (171,177). One study documented aberrant cytokine secretion when PBL from patients with RPL were stimulated *in vitro* by HLA-G bearing cells (178), whereas another study demonstrated that decidual and peripheral immune cells exhibit a shift toward the TH2 phenotype when exposed to HLA-G (179). Whether peripheral cytokine levels reflect T-helper cell dysregulation at the maternal-fetal interface or whether this dysregulation affects peripheral as well as local immune response during pregnancy remains controversial (180,181). Finally, as with all immune theories, there seems to be significant redundancy in the need for particular cytokines and soluble immunoregulatory factors at the site of implantation. To date, animal models with directed gene deletions have shown few of these factors (e.g., leukemia inhibitory factor) to be absolutely essential to pregnancy maintenance (182,183).

Although many mechanisms are aimed at avoiding maternal immune recognition of the implanting fetus, research in both humans and animals indicates that immune responses to fetal antigens can be detected (184,185,186). Thus, the regulation of this response at the maternal-fetal interface may be critical. The concept that successful pregnancy requires some form of generalized suppression of maternal immune response is supported by reports that failure to downregulate maternal responses to recall antigens, such as tetanus toxoid and influenza, is associated with poor pregnancy outcome among patients with RPL (187). Regulatory T cells as well as reproductive hormones appear important in this respect. Reproductive hormones have dramatic effects on peripheral cell-mediated immunity, as demonstrated by well-documented and notable sex differences in immune responsiveness (188). The levels of these potentially immunosuppressive hormones are elevated in pregnant women. The fact that the levels of these hormones at the maternal-fetal interface may be far above those in the maternal circulation during pregnancy (189) may explain an apparent inconsistency: overall immune responsiveness during pregnancy appears to change little, whereas local suppression at the maternal-fetal interface may be vital.

It has been suggested that the immunosuppressive effects of progesterone within the reproductive tract are at least partially responsible for the maintenance of the

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semiallogeneic implanting fetus (190). *In vitro* studies have shown that progesterone mediates its suppression of T cell effector function by alterations in membrane-resident potassium channels and cell membrane depolarization. This action, in turn, affects intracellular calcium signaling cascades and gene expression (191), and it may be mediated by nonclassical steroid receptors (192) or may not involve a receptor at all (192,193). Progesterone-mediated changes in T cell gene expression have been associated with the development of TH2-type T helper cell responses and with increased leukemia inhibitory factor expression (176,194). Because a shift in the intrauterine immune environment from TH2 to TH1 has been linked with early spontaneous pregnancy loss (171,176), the elevated intrauterine concentrations of progesterone characteristic of early pregnancy may promote an immune environment favoring pregnancy maintenance. *In vitro* evidence indicates that progesterone can inhibit mitogen-induced proliferation of and cytokine secretion by CD8⁺ T cells (195) and can alter the expression of a transcription factor that drives the development of TH1 cells (196).

Levels of estrogen increase dramatically during pregnancy, and attention has focused on the role of estrogen in immune modulation. A group of animal studies has shown that estrogens improve immune responses in males after significant trauma and hemorrhage (197), suppress cell-mediated immunity after thermal injury (198), and protect against chronic renal allograft rejection (199). *In vitro*, estrogens appear to downregulate delayed-type

hypersensitivity (DTH) reactions and promote the development of TH2-type immune responses, particularly at the elevated estrogen concentrations typical of pregnancy (200,201).

One additional regulatory mechanism proposed for the induction of maternal tolerance to the fetal allograft involves the amino acid tryptophan and its catabolizing enzyme indoleamine 2,3 dioxygenase (IDO). The IDO hypothesis of tolerance in pregnancy rests on data that T cells need tryptophan for activation and proliferation (202), and that local alterations in tryptophan metabolism at the maternal–fetal interface could either activate or fail to suppress maternal antifetal immunoreactivity (203). Recent studies in mice have shown that the inhibition of IDO leads to loss of allogeneic, but not syngeneic fetuses, and that this effect is mediated by lymphocytes (204). Further support lies in studies demonstrating that hamsters fed diets high in tryptophan have increased rates of fetal wastage (205). Extending this theory to humans requires further investigation. The expression of IDO in human uterine decidua (206) and the alterations in serum tryptophan levels with increasing gestational age during human pregnancy (207) suggest a potential local immunoregulatory mechanism.

Although associations between the development of endometriosis and immunologic abnormalities are now being defined (208), the link between endometriosis and RPL is unclear. **The occurrence of RPL in the presence of endometriosis may involve cellular or humoral dysfunction** (209,210).

Humoral Immune Mechanisms

Pregnancy-specific antigens can elicit humoral responses, and patients with RPL can display altered humoral responses to endometrial and trophoblast antigens (Table 31.2) (171,211). Nevertheless, most literature surrounding humoral immune responses and RPL focus on organ-nonspecific autoantibodies associated with APAS. Historically, these IgG and IgM antibodies were thought to be directed against negatively charged phospholipids. Those phospholipids most often implicated in RPL are cardiolipin and phosphatidylserine. Most recently, however, it has been shown that antiphospholipid antibodies often are directed against a protein cofactor, called β 2 glycoprotein 1, that assists antibody association with the phospholipid (212,213). Antiphospholipid antibodies were originally characterized by prolongation of phospholipid-dependent coagulation tests *in vitro* (activated partial thromboplastin time [aPTT], Russell Viper Venum Time) and by thrombosis *in vivo*. The association of these antiphospholipid antibodies with thrombotic complications has been

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termed the *antiphospholipid syndrome*, and although many of these complications are systemic, some are pregnancy specific—spontaneous abortion, stillbirth, intrauterine growth retardation, and preeclampsia (214). A reassessment of the criteria used to diagnose APAS resulted in the development of the Sapporo criteria, which include adverse pregnancy outcomes. These criteria, which have been validated clinically (215,216), are as follows:

Table 31.2 Concepts in Reproductive Immunology

Cellular immunity**1. Resident endometrial/decidual cells**

- a. Few B cells
- b. TCR α ; β ⁺ and TCR γ δ ⁺ cells are present, TCR γ δ ⁺ cells increase in early pregnancy
- c. NK-like, large granular lymphocytes (decidual NK cells) accumulate at sites of implantation
- d. NKT cells and "suppressor" macrophage
- e. T reg cells

2. Immune cell education and homing

- a. Thymic versus extrathymic education
- b. Possible in situ education and maintenance
- c. Integrins/vascular ligand pairs and mucosal homing

3. Antigen presentation

- a. MHC class II molecules are not expressed in the placenta
- b. Classical MHC class I molecules HLA-A and HLA-B are not expressed in the placenta
- c. Extravillous cytotrophoblast cells express HLA-C, HLA-E, and HLA-G

4. In situ immunoregulation

- a. Th1/Th2 cytokine microenvironments and dysregulation
- b. Hormonal immunomodulation
 1. Progesterone
 2. Estrogen
 3. Human chorionic gonadotropin (hCG)
 4. Prolactin
 5. Androgens
 6. Others
- c. Tryptophan metabolism and indoleamine 2,3 dioxygenase (IDO)
- d. Leukemia inhibiting factor (LIF)

Humoral immunity**1. Fetal antigens are recognized by the maternal immune system and humoral responses are mounted****2. Organ nonspecific autoantibodies**

- a. Anticardiolipin antibodies
- b. Lupus anticoagulant
- c. Anti- β glycoprotein 1 (anti- β G) antibodies
- d. Antiphosphatidylserine antibodies

3. Organ-specific autoantibodies

- a. Antithyroid antibodies
- b. Antisperm antibodies
- c. Antitrophoblast antibodies
 1. Blocking antibodies
 2. HLA sharing
 3. Trophoblast/lymphocyte cross-reactive antibodies (TLX)

NK, natural killer; NKT, natural killer T; MHC, major histocompatibility complex.

Laboratory Assessment

For a patient to be diagnosed with APAS, one or more clinical and one or more laboratory criteria must be present:

Clinical

- **One or more confirmed episode of vascular thrombosis of any type**
 - **Venous**
 - **Arterial**
 - **Small vessel**
- **Pregnancy complications**
 - **Three or more consecutive spontaneous pregnancy losses at less than 10 weeks of gestation**
 - **One or more fetal deaths at greater than 10 weeks of gestation**
 - **One or more preterm births at less than 34 weeks of gestation secondary to severe preeclampsia or placental insufficiency**

Laboratory

(Testing must be positive on two or more occasions, 6 weeks or more apart.)

- **Positive plasma levels of anticardiolipin antibodies of the IgG or IgM isotype at medium to high levels**
- **Positive plasma levels of lupus anticoagulant**

The presence of antiphospholipid antibodies (anticardiolipin or lupus anticoagulant) during pregnancy is a major risk factor for an adverse pregnancy outcome (217). In large series of couples with recurrent abortion, the incidence of the APAS was between 3% and 5% (95). The presence of anticardiolipin antibodies among patients with known systemic lupus erythematosus portends less favorable pregnancy outcome (218).

A number of mechanisms whereby antiphospholipid antibodies might mediate pregnancy loss have been proposed. Antibodies against phospholipids could increase thromboxane and decrease prostacyclin synthesis within placental vessels. The resultant prothrombotic environment could promote vascular constriction, platelet adhesion, and placental infarction (219,220,221). Alternatively, *in vitro* evidence from trophoblast cell lines indicates that IgM action against phosphatidylserine inhibits formation of syncytial trophoblast (222), which is required for proper placental function. One study demonstrated that

both extravillous cytotrophoblast and syncytiotrophoblast cells synthesize $\beta 2$ glycoprotein 1, the essential cofactor for antiphospholipid antibody binding (223). Although it gives insight into pathophysiology, the prognostic value of serum levels of specific antibodies against $\beta 2$ glycoprotein 1 with respect to pregnancy outcome among RPL patients is poorer than that of standard anticardiolipin antibodies (224,225). Some have proposed that sera from antibody-positive patients with RPL are particularly adept at inhibiting trophoblast adhesion to endothelial cells *in vitro* (226). Others have noted rapid development

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of atherosclerosis in the decidual spiral arteries of patients who test positive for antiphospholipid antibodies (227). Finally, still others have suggested that levels of the placental antithrombotic molecule—annexin V—are reduced within the placental villi from those women with RPL who test positive for antiphospholipid antibody (228). However, placental pathologic evidence supporting causal involvement of APAS in pregnancy loss often is equivocal. The lesions characteristic of this syndrome (placental infarction, abruption, and hemorrhage) often are missing in women with antiphospholipid antibodies (229), and these same lesions can be found in placentae from women with recurrent abortion who do not have biochemical evidence of antiphospholipid antibodies (230).

One additional group of autoantibodies that have been linked to RPL is the antithyroid antibodies (ATA). Although the overall significance of these antibodies is unclear (231,232), one large retrospective study showed an increased prevalence of these antibodies among women with a history of RPL, even in the absence of thyroid endocrinologic abnormalities (89). However, another study reported that the presence of serum ATA had no effect on pregnancy outcome in euthyroid pregnant patients with a history of RPL (87).

Other antibody-mediated mechanisms for recurrent abortion have been proposed, including antisperm and antitrophoblast antibodies, as well as blocking antibody deficiency. Although each hypothesis has been shown to have minimal relevance to RPL (95,154), their discussion is warranted because therapies aimed at these disorders persist. Historically, the blocking antibody deficiency hypothesis has received the most attention. This hypothesis is based on a supposition that blocking factors (presumably antibodies) were required to prevent a maternal, cell-mediated, antifetal immune response that was believed to occur in all pregnancies. It was therefore proposed that in the absence of these blocking antibodies, abortion occurred (233). This supposition has never been substantiated (234,235). For example, maternal hyporesponsiveness in mixed lymphocyte culture with paternal stimulator cells was originally proposed to identify women with deficient blocking activity (233). Investigations based on this type of testing were continued by others (236,237), who proposed that parental HLA sharing resulted in a predisposition to blocking antibody deficiency. These reports were limited by small sample size, retrospective nature, and lack of population-based controls. One prospective, population-based control study conclusively demonstrated that HLA heterogeneity was not essential for successful pregnancy (238). However, follow-up studies have now shown that, in the exceedingly rare case of complete sharing of the entire HLA region, spontaneous pregnancy losses do increase (239). This particular 10-year prospective trial concluded, however, that HLA typing is of no use in outbred populations because only isolated and significantly inbred populations have such HLA homogeneity. Further evidence refuting the blocking antibody hypothesis for recurrent abortion comes from reports of successful pregnancies both among women who do not produce serum factors capable of mixed lymphocyte culture inhibition (233) and among women who do not produce antipaternal cytotoxic antibodies (234). Those mixed lymphocyte culture results that demonstrate hyporesponsiveness in some patients with RPL are now believed to represent the effect of the pregnancy loss rather than the cause of recurrent abortion (186,233,234,235).

One final theory that arose out of the blocking antibody investigations involved a novel HLA-linked alloantigen system. The finding that polyclonal rabbit antisera could recognize both lymphocytes and trophoblast cells suggested the existence of trophoblast-lymphocyte crossreactive alloantigens (called TLX) (240). These TLX were, in turn, linked to maternal blocking antibody deficiency and RPL. The TLX hypothesis is now of historical relevance only. The theory was invalidated when TLX was found to be identical to CD46, a complement receptor that is thought to protect the placenta from complement-mediated attack (241). CD46 was not a novel alloantigen. It can be found on a wide variety of cells, thus explaining the cross-reactive nature of the original rabbit antisera.

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It is important to conclude this in-depth discussion of the immune-mediated mechanisms of isolated and recurrent pregnancy loss by suggesting that pregnancy may not require an intact maternal immune system at all. Supporting this concept are data showing that agammaglobulinemic animals and women can successfully reproduce (242). Furthermore, viable births also occur in women with severe immune deficiencies, and in murine models that lack T and B cells (severe combined immunodeficiency [SCID] mice), and in those that display a congenital absence of a thymus (nude mice). Immune factors may play important roles in a significant proportion of patients with recurrent pregnancy loss, however, and their presence is the subject of immense research to better define this role.

Other Factors

The implantation of the blastocyst within the uterine decidua represents an exquisitely scripted crosstalk between embryo and mother. Alterations in this dialogue often result in improper implantation and placental development. For instance, RPL has been linked to a dysregulation in the expression patterns of vascular endothelial growth factors (VEGF) on the developing placenta and their requisite receptors within the maternal decidua (243). Cellular and extracellular matrix adhesion properties may also be involved in this dialogue. The concept of uterine receptivity has been emboldened by the description of endometrial integrins and the timing of integrin switching during implantation (244). Others have reported decreased levels of endometrial mucin secretion (245) and reductions in the endometrial release of soluble intercellular adhesion molecule I (246) among women with histories of RPL. Programmed cell death (apoptosis) may also play an essential role in normal placental development. Alterations in two important apoptotic pathways—Fas-Fas ligand and bcl2—have been linked to RPL and poor pregnancy outcome (104,247).

A variety of environmental factors have been linked to sporadic and recurrent early spontaneous pregnancy loss. These are difficult studies to perform because, in humans, they must all be retrospective, and they are all confounded by alternative or additional environmental exposures. Nevertheless, the following factors have been linked to pregnancy loss: exposure to medications (e.g., antiprogestogens, antineoplastic agents, and inhalation anesthetics), exposure to ionizing radiation, prolonged exposure to organic solvents, and exposure to environmental toxins, especially heavy metals (248,249,250,251). Exposure to heavy metals has recently been shown to have both endocrine and immune effects that could lead to poor placentation and subsequent pregnancy loss (252). Associations between spontaneous pregnancy loss and exposures to video display terminals, microwave ovens, high-energy electric power lines, and high altitudes (e.g., flight attendants) have not been substantiated (253,254). There is no compelling evidence that moderate exercise during pregnancy is associated with spontaneous abortion. In the absence of cervical anatomic abnormalities or incompetent cervix, coitus does not appear to increase the risk of spontaneous pregnancy loss (255,256). **Exposure to three particular substances—alcohol, cigarettes, and caffeine—deserves specific attention.** Although some

conflicting data exist (257,258), one very large epidemiologic study has shown that **alcohol consumption during the first trimester of pregnancy, at levels as low as 3 drinks per week, is associated with an increased incidence of spontaneous pregnancy loss (259). Cigarette smoking has also been linked to early spontaneous pregnancy loss (260,261); however, this is also not without controversy (262). Alcohol and tobacco intake in the male partner correlates with the incidence of domestic violence, which in turn is associated with early pregnancy loss (263). Finally, a growing body of literature suggests that consumption of coffee and other caffeinated beverages during early pregnancy is related to adverse pregnancy outcome (261,264).** One highly publicized report casts doubt on the definition of a lower limit for safe use of caffeine in the first trimester of pregnancy (261). Obesity (265), stress (266), and use of nonsteroidal

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anti-inflammatory agents during early pregnancy (267,268) have all been linked to an increased rate of isolated spontaneous pregnancy loss.

Preconception Evaluation

Evaluation of recurrent spontaneous abortion should include obtaining a thorough history from both partners, performing a physical assessment of the woman (with attention to the pelvic examination), and a limited amount of laboratory testing (Table 31.3).

History

A description of all prior pregnancies and their sequence, as well as whether histologic assessment and karyotype determinations were performed on previously aborted tissues, is an important aspect of the history. **Approximately 60% of abortuses lost before 8 weeks of gestation have been reported to be chromosomally abnormal (269); most of these pregnancies are affected by some type of trisomy, particularly trisomy 16 (270). The most common single chromosomal abnormality is monosomy X (45X), especially among anembryonic conceptuses (271).** Aneuploidy may be detected less often in miscarriage specimens when the couple experiencing recurrent abortions is euploidic. Alternatively, some investigators have suggested that because aneuploidy is common among miscarriage specimens from patients experiencing both isolated and recurrent spontaneous pregnancy losses, the documentation of aneuploidy in tissues from patients with RPL does not affect their prognosis for future pregnancy maintenance (9).

Most women with RPL tend to experience spontaneous abortion at approximately the same gestational age in sequential pregnancies. Unfortunately, the gestational age when pregnancy loss occurs, as determined by last menstrual period, may not be informative because there is often a 2- to 3-week delay between fetal demise and signs of pregnancy expulsion (272). The designation of couples into primary or secondary categories also is not helpful for either the diagnosis or management in most cases. Approximately 10% to 15% of couples cannot be classified into either primary or secondary categories, because although their first pregnancy resulted in a loss, it was followed by a term delivery before subsequent losses.

It is important to elicit any history of subfertility or infertility among couples with RPL. This condition is defined by the inability to conceive after 12 months of unprotected intercourse. By definition, 15% of all couples will meet this criteria; this number increases to 33% among couples with RPL. Because many pregnancies are lost before or near the time of missed menses, subfertility among patients with RPL may, in some cases, reflect recurrent preclinical losses. Menstrual cycle history may provide

information about the possibility of oligo-ovulation or other relevant endocrine abnormalities in patients with RPL. An assessment of the timing of intercourse relative to ovulation should be reviewed with couples in an effort to detect dyssynchronous fertilization that could contribute to pregnancy loss (273). A personal and family history of thrombotic events or renal abnormalities may provide vital information. A family history of pregnancy losses and obstetric complications should be discussed specifically. Detailed information about drug and environmental exposure should also be obtained.

Physical Examination

A general physical examination should be performed to detect signs of metabolic illness, including PCOS, diabetes, hyperandrogenism, and thyroid or prolactin disorders. During the pelvic examination, signs of infection, DES exposure, and previous

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trauma should be ascertained. Estrogenization of mucosal tissues, cervical and vaginal anatomy, and the size and shape of the uterus should also be determined.

Table 31.3 Investigative Measures Useful in the Evaluation of Recurrent Early Pregnancy Loss

History
1. Pattern, trimester, and characteristics of prior pregnancy losses
2. History of subfertility or infertility
3. Menstrual history
4. Prior or current gynecologic or obstetric infections
5. Signs or symptoms of thyroid, prolactin, glucose tolerance and hyperandrogenic disorders (including PCOS)
6. Personal or familial thrombotic history
7. Features associated with the antiphospholipid syndrome (thrombosis, false positive test for syphilis)
8. Other autoimmune disorders
9. Medications
10. Environmental exposures, illicit and common drug use (particularly caffeine, alcohol, cigarettes, and in utero DES exposure)
11. Genetic relationship between reproductive partners
12. Family history of recurrent spontaneous abortion, obstetric complications, or any syndrome associated with embryonic or fetal losses
13. Previous diagnostic tests and treatments
Physical Examination
General physical examination with particular attention to:
1. Obesity
2. Hirsutism/acanthosis
3. Thyroid examination
4. Breast examination/galactorrhea
5. Pelvic examination

a. Anatomy
b. Infection
c. Trauma
d. Estrogenization
e. Masculinization
Laboratory
1. Parental peripheral blood karyotype
2. Hysterosalpingography or office hysteroscopy, followed by hysteroscopy/laparoscopy, if indicated
3. Thyroid-stimulating hormone level, serum prolactin level if indicated
4. Anticardiolipin antibody level
5. Lupus anticoagulant (activated partial thromboplastin time or Russell Viper Venom)
6. Complete blood count with platelets
7. Factor V Leiden, G20210A prothrombin gene mutation, protein S activity, homocysteine level, activated protein C resistance
8. Protein C activity, antithrombin level if personal or family history of VTE
PCOS, polycystic ovarian syndrome; DES, diethylstilbestrol; VTE, venous thromboembolism.

Laboratory Assessment

Valuable Tests

Laboratory assessment of couples with RPL should include the following tests:

- **Parental peripheral blood karyotyping with banding techniques**
- **Assessment of the intrauterine cavity with either office hysteroscopy, sonohysterography or hysterosalpingography, followed by operative hysteroscopy if a potentially correctable anomaly is found**
- **Thyroid function testing, including serum thyroid-stimulating hormone levels**
- **Anticardiolipin antibody and lupus anticoagulant testing (aPTT or Russell Viper Venom testing)**
- **Thrombophilia testing:**
- **Factor V Leiden, G20210A prothrombin gene mutation, protein S activity**
- **Serum homocysteine levels**
- **In the presence of a family or personal history of VTE, protein C and antithrombin activity**

- **Possible alterations based on ethnic background: Factor V Leiden and prothrombin are rare in African and Asian populations; Protein C and S are the most common inherited thrombophilias in Chinese populations**
- **Platelet levels**

Tests with Unproven Utility

A number of laboratory assessments are being evaluated for use in patients with a history of RPL. At present, results are either too preliminary to warrant recommendation or the results of studies have been too contradictory to allow final determination of their value. **Tests with unproven or unknown utility include:**

- **Evaluation of ovarian reserve using day 3 serum follicle-stimulating hormone levels or the clomiphene challenge test is of limited value because decreased ovarian reserve may portend poor outcome in all patients, including those with RPL (274,275).**
- **Testing for serologic evidence of PCOS using luteinizing hormone or androgen values may be useful (77,78,79,80,276).**
- **Testing for peripheral evidence of TH1/TH2 cytokine dysregulation may be of value.** Although large studies have failed to demonstrate an association between peripheral cytokine alterations and pregnancy outcome among patients with RPL (180), smaller studies have reported peripheral shifts toward TH1 profiles only in those patients with RPL who subsequently lose their pregnancy (181). One study documented a shift toward TH1 profiles at the time of fetal demise in these patients; however, it is difficult to determine a cause-and-effect relationship (277).

- **Preconceptional testing for the prevalence and activity of peripheral NK cells has been reported in small studies to help determine the prognosis and to assist with patient counseling (278,279).** Still, peripheral NK cells may not adequately represent those at the site of implantation, and this testing remains unproven.
- **Testing for antithyroid antibodies, even among women with RPL who are euthyroid, remains controversial.** Although some have shown no association between the presence of antithyroid antibodies and recurrent loss (231), others have demonstrated an increased prevalence among patients with a history of RPL (89,232). However, even if the prevalence of antithyroid antibodies is increased among these patients, the significance of their presence is questionable (87).
- **Testing for the presence of a variety of autoantibodies (other than lupus anticoagulant and anticardiolipin antibody) has been hotly debated without consensus (280,281).** Testing for some antiphospholipid antibodies, such as antiphosphatidylserine and anti- β 2 glycoprotein 1 (anti- β 2g), is compelling because their

presence has been connected to placental pathology (222,223,224,225). One recent, large series has shown anti- β 2g to be associated with risk for RPL (282). In patients with known autoimmune diseases and RPL, additional antiphospholipid testing may be warranted (283).

- **Cervical cultures for mycoplasma, ureaplasma, and chlamydia may be considered.**

- **The Noyes criteria has low interobserver reproducibility and accuracy and thus cannot reliably be used to diagnose a luteal phase defect on timed endometrial biopsy (284).** This tool lacks precision and does not alter clinical management (285).

The following investigations have no place in the care of patients with recurrent spontaneous pregnancy loss:

- Evaluations that involve extensive testing for serum or site-specific auto- or alloantibodies (including antinuclear antibodies and antipaternal cytotoxic antibodies) are both expensive and unproven. Their use often serves only to verify the statistical tenet that if the number of tests performed reaches a critical limit, the results of at least one will be positive in every patient.

- Testing for parental HLA profiles is never indicated in outbred populations. The association of HLA sharing with poor pregnancy outcomes is applicable only to those populations that have very high and sustained levels of marriage within a limited community (239).

- Use of mixed lymphocyte cultures has not proven useful. Use of other immunologic tests also is unnecessary unless these studies are performed, with informed consent, under a specific study protocol in which the costs of these experimental tests are not borne by the couple or their third-party payers.

- Suppressor cell factor determinations; cytokine, oncogene, and growth factor measurements; and embryotoxic factor assessment are not clinically justified.

Postconception Evaluation

Following conception, patients with histories of RPL should be monitored closely to provide psychological support and to confirm intrauterine pregnancy and its viability.

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The incidence of ectopic pregnancy (286,287) and complete molar gestation (287,288) is increased in women with a history of recurrent spontaneous pregnancy loss.

Although somewhat controversial (289), some data suggest that the risk of pregnancy complications other than spontaneous abortion are not significantly different between women with and those without a history of recurrent losses (89,290). Two exceptions to this observation are women who have antiphospholipid antibodies and those who have an intrauterine infection.

Determining serum levels of β -human chorionic gonadotropin (hCG) may be helpful in monitoring early pregnancy until an ultrasonographic examination can be performed; however, inadequate β -hCG levels do not always occur in pregnancies that ultimately abort (291). Other hormonal determinations are rarely of benefit because levels are often normal until fetal death or abortion occurs (292). The best method for monitoring

in early pregnancy is ultrasonography.

Serial ultrasonography and a variety of hormonal and biochemical measurements during early pregnancy have prognostic value in women with histories of recurrent losses (293). If used, **serum β -hCG levels should be monitored serially from the time of a missed menstrual period until the level is approximately 1,200 to 1,500 mIU/mL, at which time an ultrasonographic scan is performed and blood sampling is discontinued.** Ultrasonographic assessment may then be performed every 2 weeks until the gestational age at which previous pregnancies were aborted. If pregnancy has been confirmed but fetal cardiac activity cannot be documented by approximately 6 to 7 weeks of gestation (by sure menstrual or ultrasonographic dating), intervention is recommended to expedite pregnancy termination and to obtain tissue for karyotype analysis. Nuchal lucency measurement (11–12 weeks) and/or maternal serum analysis (with nuchal lucency and/or at 15–18 weeks) may be used for prenatal assessment. Amniocentesis may be recommended to assess the fetal karyotype after the pregnancy has progressed past the time of prior losses.

The importance of obtaining karyotypic analysis from tissues obtained after pregnancy demise in a woman experiencing recurrent losses cannot be overemphasized. Results may suggest karyotypic anomalies in the parents. The documentation of aneuploidy may have important prognostic implications and may direct future interventions. Karyotypic analysis is financially prudent among patients with histories of RPL (294). Obtaining karyotypic data from aborted specimens is complicated by difficulties in culturing cells from tissues that may have significant inflammation or necrosis and contamination of specimens with maternal cells. Efforts to develop methods that avoid such difficulties include the application of comparative genomic hybridization technology to RPL (295). This technology has even been used successfully with archived and paraffin-embedded pregnancy tissues (296). In the future, fetal karyotype assessment may also be performed using DNA isolated from nucleated fetal erythrocytes in maternal blood (297).

Therapy

Advances in the treatment of patients with RPL have been regrettably slow. Although there has been a rapid expansion in knowledge of the molecular and subcellular mechanisms involved in implantation and early pregnancy maintenance, extension of these concepts to prevention of RPL has lagged. In addition to these limitations, progress toward treatment of most causes of RPL has been hampered by a variety of factors. The condition itself has not been defined consistently. **The results of clinical trials involving patients with RPL patients are, therefore, often nearly impossible to compare and evaluate.** Trial design is frequently substandard, with lack of rationale, lack of appropriate controls, and poor statistical analysis limiting the ability to draw rational conclusions from reported results. Finally, epidemiologic data indicate that most patients with a history of RPL will,

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in fact, have a successful pregnancy the next time they conceive (5). For these reasons, with few exceptions, most therapies for RPL must be considered experimental. Until further study is completed, treatment protocols involving these therapies should be undertaken only with informed consent and in the setting of a well-designed, double-blinded, placebo-controlled clinical trial.

Common therapeutic options that currently exist for patients with RPL include the use of donor oocytes or sperm, the use of preimplantation genetic diagnosis, the use of antithrombotic interventions, the repair of anatomic anomalies, the correction of any endocrine abnormalities, the treatment of infections, and a variety of

immunologic interventions and drug treatments. Psychological counseling and support is recommended for all patients.

Genetic Abnormalities

No therapies are presently available to treat those parental chromosomal anomalies that potentially contribute to recurrent abortion. Three alternative approaches exist when genetic factors are linked to RPL. Some approaches, **such as antithrombotic therapy** for patients with inherited thrombophilias, are directed to the effects of the genetic abnormality. Other techniques, such as **preimplantation genetic diagnosis**, attempt to identify those particular embryos that are affected by chromosomal disorders and select against them. **Recent evidence suggests that in women with a history of three or more spontaneous pregnancy losses, a subsequent pregnancy loss has a 58% risk of chromosomal abnormality (298). If the incidence of chromosomal abnormalities among the conceptuses of patients with RPL is this high, it could be argued that the use of assisted reproductive technologies, including preimplantation genetic diagnosis, might be indicated for all patients with unexplained RPL.**

Preimplantation genetic diagnosis involves the removal of a single cell from an *in vitro*-matured embryo. Genetic testing can be performed on this cell to rule out gross chromosomal abnormalities or the presence of specific genetic diseases (e.g., cystic fibrosis). Embryos that are diagnosed with genetic abnormalities are not replaced into the uterine cavity. Those demonstrated to be genetically normal would be considered appropriate for transfer into the uterus. Use of preimplantation genetic diagnosis, therefore, has the potential to dramatically reduce the incidence of pregnancy loss arising from a genetic cause. Use of preimplantation genetic diagnosis in patients with known heritable genetic disorders (e.g., cystic fibrosis, X-linked disorders) is presently in widespread use. Women with a history of RPL have a higher incidence of aneuploid embryos than those without a history of losses (298,299). For this reason, RPL has recently been considered as a reasonable indication for the use of *in vitro* fertilization with preimplantation genetic diagnosis. The efficacy of this technique in the treatment of patients with RPL continues to be investigated (300,301).

The third approach to patients with genetic factors and RPL is particularly relevant to those with Robertsonian translocations involving homologous chromosomes. In these patients, their genetic anomaly always results in embryonic aneuploidy. Therefore, **use of either donor oocyte or donor sperm, depending on the affected partner, is recommended.** Use of donor gametes among patients with a history of RPL has been shown to be as effective as its use in matched patients without such a history (302). Synchronization of intercourse with ovulation may benefit some patients with genetic factor RPL (273). In all cases, genetic counseling is warranted.

Anatomic Anomalies

Hysteroscopic resection represents state-of-the-art therapy for submucous leiomyomas, intrauterine adhesions, and intrauterine septa. This approach appears to limit

postoperative sequelae while maintaining efficacy in terms of reproductive outcome (67,69). Use may even be safely extended to patients with DES exposure, hypoplastic uteri, and complicating septal anomalies (67,69,303). Attempts to improve on standard hysteroscopic metroplasty, which typically is performed in the operating room using general anesthesia, often with laparoscopic guidance, are presently under investigation. Ultrasonographically guided transcervical metroplasty has been reported to be safe and effective (304). Ambulatory, office-based procedures (305), including septum

resection under fluoroscopic guidance (306), also are options.

For patients with a history of loss secondary to cervical incompetence, placement of a cervical cerclage is indicated. This procedure usually is performed early in the second trimester after documentation of fetal viability. Cervical cerclage should be considered as a primary intervention for women with DES-associated uterine anomalies. If endometriosis is encountered during a diagnostic evaluation, it should be resected laparoscopically.

Endocrine Abnormalities

Some investigators have proposed the use of ovulation induction for the treatment of RPL based on the hypothesis that ovulation induction is associated with healthier oocytes (307,308). Healthier oocytes, in turn, may decrease the incidence of luteal phase insufficiency, which should result in improved pregnancy maintenance. This approach grossly oversimplifies the mechanisms involved in implantation and early pregnancy maintenance. Empiric use of empiric ovulation induction for treatment of unexplained RPL should be viewed with caution because recent evidence from small studies indicates such use is not effective (308). In some subsets of patients with RPL, use of ovulation induction could be of benefit. For instance, stimulating folliculogenesis with ovulation induction or luteal phase support with progesterone should be considered for women with luteal phase insufficiency. The efficacy of these therapies, however, has never been substantiated (309). Ovulation induction might also be beneficial for women with hyperandrogen and LH hypersecretion disorders, especially following pituitary desensitization with gonadotropin-releasing hormone agonist therapy (95). This treatment also remains controversial; according to findings from the only large, prospective, randomized controlled trial to date, neither prepregnancy pituitary suppression nor luteal phase progesterone supplementation has therapeutic efficacy (310).

Based on the association between PCOS, hyperandrogenism, hyperinsulinemia, and RPL (77,78,79,80), there has been increasing support for the use of insulin-sensitizing agents in the treatment of RPL that occurs in the presence of PCOS (311,312). Prepregnancy glycemic control may be particularly important for women with overt diabetes mellitus (81,82). Thyroid hormone replacement with *Synthroid* may be helpful in cases of hypothyroidism. There is no place in the medical management of recurrent abortion for either thyroid medication or *bromocriptine* for women who do not have a thyroid or prolactin disorder.

Infections

Empiric antibiotic treatment has been used for couples with recurrent abortion, despite its unproven efficacy. **Elaborate testing for infectious factors and use of therapeutic interventions is not justified unless a patient is immunocompromised or a specific infection has been documented** (96). For cases in which an infectious organism has been identified, appropriate antibiotics should be administered to both partners, followed by posttreatment cultures to verify eradication of the infectious agent before attempting conception.

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Immunologic Factors

Immune-mediated RPL has received more attention than any other single etiologic classification. Nevertheless, techniques for diagnosis and treatment of most cases remains unclear (154,313,314,315). **Most therapies for proposed immune-related RPL must be considered experimental.** As stated earlier, it is known that the developing conceptus

contains paternally inherited gene products and tissue-specific differentiation antigens and that maternal recognition of these antigens occurs (184,185,186). Historically, it has been speculated that both inappropriately weak immune responses to these antigens and unusually strong responses could result in early pregnancy loss. As a consequence, both immunostimulating and immunosuppressive therapies have been proposed.

Immunostimulating Therapies: Leukocyte Immunization

Stimulation of the maternal immune system using alloantigens on either paternal or pooled donor leukocytes has been promoted for patients with immune RPL, and a number of reports support possible mechanisms for potential therapeutic value (316,317,318,319). Both individual clinical trials and meta-analyses, however, report conflicting results concerning the efficacy of leukocyte alloimmunization in patients with RPL (320,321,322,323,324,325). This lack of consensus most certainly reflects the remarkable heterogeneity in study design, patient selection, and therapeutic protocols, as well as the typically small numbers of enrolled subjects in these investigations. One published analysis reports that approximately 11 women with unexplained recurrent abortion would need to be immunized with alloantigenic lymphocytes before one additional live birth was achieved (322). Approximately 92% of successful pregnancy outcomes in this study were not attributable to leukocyte immunization. Whether the 8% successful pregnancy rate achieved in leukocyte-immunized women is clinically relevant remains uncertain. **One of the largest trials evaluating the efficacy of leukocyte immunization in patients with unexplained RPL is a part of the *Recurrent Miscarriage (REMIS)* study (324). This large (more than 90 patients per treatment arm), prospective, placebo-controlled, randomized, double-blinded investigation showed no efficacy for paternal leukocyte immunization in couples with unexplained RPL. A Cochrane review of 19 well-designed trials of immunotherapy for RPL found no evidence that paternal or allogeneic leukocyte immunization altered pregnancy outcome in women with otherwise unexplained RPL (326). Leukocyte immunization also poses significant risk to both the mother and her fetus (296,297). Several cases of graft-versus-host disease, severe intrauterine growth retardation, and autoimmune and isoimmune complications have been reported (321,322,327,328,329,330). In addition, alloimmunization to platelets contained in the paternal leukocyte preparation has been associated with cases of potentially fatal fetal thrombocytopenia. **The routine use of this therapy for recurrent abortion (that, at best, will only be efficacious in one of 11 women treated) cannot be clinically justified at present. The procedure should be performed only as part of an appropriately controlled trial using informed consent.** Other immunostimulating therapies have been proposed and abandoned. Intravenous preparations consisting of syncytiotrophoblast microvillus plasma membrane vesicles have been used to mimic the fetal cell contact with maternal blood that normally occurs in pregnancy (331). The efficacy of this therapy has not been established (326,331). The use of third-party seminal plasma suppositories has also been attempted (332), based on the misconception that TLX was part of an idio-anti-idiotypic control system (333). Third-party seminal plasma suppositories for recurrent abortion have no scientifically credible rationale and should not be used.**

Immunosuppressive Therapies

Immunosuppressive and other immunoregulating therapies have been advocated for cases in which abortion was believed to be due to antiphospholipid antibodies or to inappropriate cellular immunity toward the implanting fetus. Again, study design problems, including small numbers of recruited patients, lack of prestratification by maternal age and number of prior losses before randomization, and other methodologic and statistical inaccuracies,

preclude definitive statements regarding therapeutic efficacy for most of the proposed immunosuppressive approaches.

Intravenous Immunoglobulin

Intravenous immunoglobulins (IVIg) are composed of pooled samples of immunoglobulins harvested from a large number of blood donors. Studies on the use of IVIg therapy in the treatment of RPL are based on the theory that some patients have an overzealous immune reactivity to their implanting fetus. Although IVIGs do have immunosuppressive effects, the mechanisms underlying this immune modulation are only partially understood. These mechanisms may include decreased autoantibody production and increased autoantibody clearance, T cell and Fc receptor regulation (334), complement inactivation (335), enhanced T cell suppressor function, decreased T-cell adhesion to the extracellular matrix (336), and downregulation of TH1 cytokine synthesis (337). **Based on a large number of relatively small studies using a variety of treatment protocols, there remains no conclusive evidence to suggest that use of IVIg in the treatment of patients with unexplained (and presumed immunologic) RPL has any benefit** (338,339,340,341,342). **The Cochrane review of immune therapy for RPL also addressed IVIg therapy and reported that its use did not alter pregnancy outcomes in patients with otherwise unexplained RPL** (326). Improved posttreatment pregnancy rates may be seen when IVIg is used in those specific patients with autoimmune-mediated pregnancy loss associated with APAS (343,344). Therapy with IVIGs for RPL is expensive, invasive, and time-consuming, requiring multiple intravenous infusions over the course of pregnancy. Side effects of IVIg therapy include nausea, headache, myalgias, and hypotension. More serious adverse effects include anaphylaxis (particularly in patients with IgA deficiency) (345).

Progesterone

As mentioned earlier, progesterone also has known immunosuppressive effects (188,189,190,191,195,196). **A number of studies using *in vitro* cellular systems relevant to the maternal-fetal interface have now shown that progesterone either inhibits TH1 immunity or causes a shift from TH1 to TH2-type responses** (176,194,195,196,346,347). Progesterone has been administered both intramuscularly and intravaginally for the treatment of RPL. It is thought that vaginal administration may increase local, intrauterine concentrations of progesterone better than systemic administration. Vaginal formulations may, therefore, provide a better method of attaining local immunosuppressive levels of progesterone while averting any adverse systemic side effects. **Although both vaginal and intramuscular progesterone therapy are associated with few minor side effects, their efficacy in the treatment of either unexplained RPL or RPL associated with TH cell dysregulation has never been investigated appropriately.**

Other immunoregulating therapies theoretically useful in treating RPL include the use of cyclosporine, pentoxifylline, and nifedipine, although maternal and fetal risks with these agents preclude their clinical use. Plasmapheresis has also been used to treat women with recurrent abortion and antiphospholipid antibodies (348). Generalized immunosuppression with corticosteroids, such as prednisone, has been advocated during pregnancy for women with recurrent losses and chronic intervillitis (349) and APAS. Although corticosteroids have shown some promise in these patients (349,350), maternal and fetal side effects and the availability of alternative therapies have limited their use. **The efficacy and side effects**

of prednisone plus low-dose *aspirin* was examined in a recent, large, randomized, placebo-controlled trial treating patients with autoantibodies and RPLs. Pregnancy outcomes for treated and control patients were similar; however, the incidence of maternal diabetes and hypertension and the risk of premature delivery were all increased among those treated with prednisone and *aspirin* (351).

Antithrombotic Therapy

Therapy for patients with RPLs associated with either APAS or other thrombophilic disorders has focused on the use of antithrombotic medications.

Unlike immunosuppressive treatments, this approach mainly treats the effect (hypercoagulability) but not the underlying cause (e.g., genetic, APAS) of RPL. However, there are reports that *heparin*, a typical anticoagulant, may exert direct immunomodulatory effects by binding to antiphospholipid antibodies (352) and may decrease movement of inflammatory cells

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to sites of alloantigen exposure (353). **The combined use of low-dose *aspirin* (75–80 mg/day) and subcutaneous unfractionated *heparin* (5,000–10,000 units twice daily) during pregnancy has been best studied among women with APAS and appears to be efficacious** (354,355,356). A typical regimen for women with antiphospholipid antibody syndrome would include use of *aspirin* (80 mg every day) beginning with any attempts to conceive. After pregnancy has been confirmed, 10,000 IU unfractionated *sodium heparin* is administered subcutaneously twice daily, throughout gestation. An aPTT should be obtained weekly, and dosages of *heparin* should be adjusted until anticoagulation is achieved. Patients using this therapy should be treated in conjunction with a perinatologist because of their increased risks of preterm labor, premature rupture of the membranes, intrauterine growth restriction, intrauterine fetal demise, and preeclampsia. Other potential risks include gastric bleeding, osteopenia, and abruptio placenta.

The effectiveness of antithrombotic therapy in the treatment of patients with APAS and RPL has led to efforts to expand treatment in new directions. These directions include the use of *low-molecular weight heparin (LMWH)*, the use of antithrombotic therapy in patients with thrombophilia and RPL who do not have APAS, and even the use of such therapy among patients with RPL who do not have thrombophilia (unexplained recurrent losses).

Low-molecular weight heparin is superior to unfractionated heparin in the treatment of many clotting disorders (357,358). *Low-molecular weight heparin* has the advantage of an increased antithrombotic ratio when compared with unfractionated *heparin*. This characteristic results in improved treatment of inappropriate clotting but fewer bleeding side effects. In addition, LMWH has been associated with a decreased incidence of thrombocytopenia and osteoporosis when compared with its unfractionated counterpart. Finally, LMWH has a long half-life and requires less frequent dosing and monitoring, thereby improving patient compliance. **Although its safe use in pregnancy is still being evaluated, LMWH has shown promise when combined with low-dose *aspirin* in the treatment of RPL associated with APAS** (355). One study comparing the use of unfractionated *heparin* and *aspirin* to LMWH and *aspirin* in the treatment of women with APAS and adverse pregnancy outcomes showed the therapies had similar effects (359). Efficacy has also been suggested for similar treatment of RPL associated with other thrombophilias, including activated protein C resistance associated with factor V Leiden, mutations in the promoter region of the prothrombin gene, and decreases in protein C and protein S activities (359,360,361,362,363). The use of LMWH for this indication appears to have an excellent safety profile for mother and fetus (364,365).

The prophylactic use of daily low-dose *aspirin* has become common practice based on its

perceived cardiovascular effects combined with its low incidence of side effects. Its sole use in the treatment of RPL has likewise gained momentum, and many patients with histories of recurrent loss will either self-prescribe this therapy or will inquire about its usefulness. At present, there are no good data supporting its use either in patients with heritable thrombophilias or in the general RPL population. In fact, although studies are small, **the use of low-dose aspirin alone has not been shown to be effective in the treatment of RPL associated with APAS** (366,367). In these patients, it should be used in combination with unfractionated or low-molecular-weight *heparin*. One large study evaluating the therapeutic efficacy of empiric use of low-dose *aspirin* among 805 patients with unexplained RPL concluded that such therapy cannot be justified in patients with early losses but may benefit patients with second trimester losses (367).

Reports of an increased incidence of isolated spontaneous pregnancy loss with the use of aspirin in early pregnancy have raised questions about this practice (368,369). These reports are poorly designed and do not adequately address the level of exposure (81 mg versus 325 mg). At this time, **aside from use in combination with heparin for patients with RPL and APAS, and in patients with late losses, aspirin should be avoided during early pregnancy.**

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More directed antithrombotic therapies have also been described for the treatment of RPL among patients with thrombophilias. For instance, the use of protein C concentrates has been associated with favorable pregnancy outcome in a patient with a history of thrombosis, recurrent fetal losses, and protein C deficiency (370).

As mentioned previously, vitamins B₆, B₁₂, and folate are important in homocysteine metabolism (15,18), and hyperhomocysteinemia is linked to RPL (17,25,62). Women with RPL and isolated fasting hyperhomocysteinemia should be offered supplemental folic acid (0.4–1.0 mg/day), vitamin B₆ (6 mg/day), and possibly vitamin B₁₂ (0.025 mg/day) (371,372,373,374). Fasting homocysteine levels should be retested after treatment. If levels are normalized or remain only marginally elevated, no further therapy is necessary. Homocysteine levels will predictably decrease during pregnancy.

Treatment of women with RPL and an identified inherited or acquired thrombophilia should be based on their history:

- **If venous thromboembolism occurs during the index pregnancy, posthospitalization management requires therapeutic anticoagulation:**
 - Unfractionated heparin: 10,000 to 15,000 U subcutaneously every 8 to 12 hours (monitor to keep aPTT 1.5–2.5 times normal), or
 - LMWH: *enoxaparin* 40 to 80 mg subcutaneously twice daily or *dalteparin* 5,000 to 10,000 U subcutaneously twice daily. Consider monitoring trough factor Xa levels in the third trimester.
- **If there is a personal history of venous thromboembolism (particularly in previous pregnancy or with hormonal contraceptive use) or a strong thrombophilic family history, treat with therapeutic anticoagulation.**
- **If combined thrombophilic defects are detected, treat with therapeutic anticoagulation.**
-

If an isolated thrombophilic defect is detected and there is no personal or strong family history of thrombotic complications, consider prophylactic anticoagulation:

- **—Unfractionated *heparin*: 5,000 U subcutaneously twice daily (first trimester), 7,500 U subcutaneously twice daily (second trimester), and 10,000 U subcutaneously (third trimester)**
- **—LMWH: *enoxaparin* 40 mg subcutaneously daily or *dalteparin* 5,000 U subcutaneously daily**
- **Consider prophylactic anticoagulation in women with RPL and hyperhomocysteinemia refractory to dietary intervention. Therapy should be initiated with documentation of pregnancy. There are no data suggesting initiation preconceptionally improves outcomes.**

Thrombotic risk is greatest during the postpartum period. Anticoagulation should be reinitiated after delivery in doses reflecting predelivery treatment regimens. Postpartum anticoagulation should be continued for 6 to 12 weeks postpartum. Women may continue injectable therapy or transition to oral anticoagulants (e.g., *coumarin*). Use of *heparin* or of *coumarin* derivatives does not prohibit breastfeeding.

Psychological Support

Experiencing isolated or recurrent losses can be emotionally devastating. The risk of major depression is increased greater than twofold among women with spontaneous pregnancy loss; in most women it arises in the first weeks following delivery (375). A caring and empathetic attitude is prerequisite to all healing. The acknowledgment of the pain and suffering couples have experienced as a result of recurrent abortion can be

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a cathartic catalyst enabling them to incorporate their experience of loss into their lives rather than their lives into their experience of loss (95). **Referrals to support groups and counselors should be offered.** Self-help measures, such as meditation, yoga, exercise, and biofeedback may also be useful.

Prognosis

The prognosis for successful pregnancy depends both on the potential underlying cause of pregnancy loss and (epidemiologically) on the number of prior losses (Table 31.4). As previously discussed, epidemiologic surveys indicate that the chance of a viable birth even after four prior losses may be as high as 60%. Depending on the study, **the prognosis for successful pregnancy in couples with a cytogenetic basis for reproductive loss varies from 20% to 80%** (376,377,378). **Women with corrected anatomical anomalies may expect a successful pregnancy in 60% to 90% of cases** (376,377,379,380). **A success rate higher than 90% has been reported for women with corrected endocrinologic abnormalities** (376). **Between 70% and 90% of pregnancies reported among women receiving therapy for antiphospholipid antibodies have been viable** (381,382).

Many forms of pre- or postconceptional tests have been proposed to help

predict pregnancy outcome (172,187,279,383,384); none has been fully substantiated in large, prospective trials. The documentation of fetal cardiac activity with ultrasonography may offer prognostic value; however, it appears that predictions may be greatly affected by any underlying diagnosis. In one study, the live birth rate following documentation of fetal cardiac activity between 5 and 6 weeks from the last menstrual period was approximately 77% in women with two or more unexplained spontaneous abortions

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(385). It may be important to note that most of the patients in this study had evidence of inappropriate antitrophoblast cellular immunity. Others have shown that 86% of patients with antiphospholipid antibodies and RLP had fetal cardiac activity detected before subsequent demise (386). Most recently, however, **a prospective, longitudinal, observational study of 325 patients with unexplained RLP showed that only 3% of 55 miscarriages occurred following the detection of fetal cardiac activity using transvaginal ultrasonography (387).**

Table 31.4 Prognosis for a Viable Birth

Following:	
One spontaneous loss	76%
Two spontaneous losses	70%
Three spontaneous losses	65%
Four spontaneous losses	60%
With:	
Genetic factors	20%–80%
Anatomic factors	60%–90%
Endocrine factors	>90%
Infectious factors	70%–90%
Antiphospholipid antibodies	70%–90%
Th1 cellular immunity	70%–87%
Unknown factors	40%–90%
Following detection of fetal cardiac activity:	
Unexplained RPL	77%–97%
APAS and RPL	Much lower

RPL, recurrent pregnancy loss; APAS, antiphospholipid antibody syndrome.

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Menopause

Jan L. Shifren

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- **Vasomotor symptoms affect up to 75% of perimenopausal women. Symptoms last for 1 to 2 years after menopause in most women but may continue for 10 years or longer in some others.**
- **Topical vaginal application of low doses of estrogen is an effective and safe treatment of vaginal dryness, dyspareunia, and some urinary symptoms.**
- **Counseling women to alter modifiable risk factors is important for both the prevention and treatment of osteoporosis. Many women have diets deficient in calcium and vitamin D and will benefit from dietary changes and supplementation. Women should receive 1,000 to 1,500 mg of calcium**

and 400 to 800 IU of vitamin D daily.

Contraindications to hormone therapy use include known or suspected breast or endometrial cancer, undiagnosed abnormal genital bleeding, active thromboembolic disorders, and active liver or gallbladder disease. Relative contraindications include heart disease; migraine headaches; and previous liver or gallbladder disease, or endometrial cancer, or thromboembolic events.

Menopause, the permanent cessation of menstruation, occurs at a mean age of 51 years. Despite a great increase in the life expectancy of women, the age at menopause has remained remarkably constant. **A woman in the United States today will live approximately 30 years, or greater than a third of her life, beyond the menopause.** After menopause, the ovaries cease to produce significant amounts of estrogen; therefore, symptoms and diseases associated with estrogen deficiency are of increasing importance to women's health.

The age at menopause appears to be genetically determined and is unaffected by race, socioeconomic status, age at menarche, or number of prior ovulations. Factors that are toxic to the ovary often result in an earlier age of menopause; women who smoke experience an earlier menopause (1), as do many women exposed to chemotherapy or

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pelvic radiation. Women who have had surgery on their ovaries, or have had a hysterectomy, despite retention of their ovaries, also may experience early menopause (2). **Premature ovarian failure, defined as menopause before the age of 40 years, occurs in approximately 1% of women.** It may be idiopathic or associated with a toxic exposure, chromosomal abnormality, or autoimmune disorder.

Although menopause is associated with changes in the hypothalamic and pituitary hormones that regulate the menstrual cycle, menopause is not a central event, but rather primary ovarian failure. At the level of the ovary, there is a depletion of ovarian follicles, most likely secondary to apoptosis or programmed cell death. The ovary, therefore, is no longer able to respond to the pituitary hormones, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), and ovarian estrogen and progesterone production cease.

Androgen production from the ovary continues beyond the menopausal transition because of sparing of the stromal compartment. Androgen concentrations are lower in menopausal women than in women of reproductive age. This finding appears to be associated more with aging and decreased functioning of the ovary and adrenal glands over time rather than with menopause per se. Menopausal women continue to have low levels of circulating estrogens, principally from peripheral aromatization of ovarian and adrenal androgens. Adipose tissue is a major site of aromatization, so obesity affects many of the sequelae of menopause. **The ovarian-hypothalamic-pituitary axis remains intact during the menopausal transition; thus, FSH levels rise in response to ovarian failure and the absence of negative feedback from the ovary.** Atresia of the follicular apparatus, in particular the granulosa cells, results in reduced production of estrogen and inhibin, resulting in reduced inhibin levels and elevated FSH levels, a cardinal sign of menopause.

Several staging systems have been developed to describe the many changes that encompass the transition from reproductive life to postmenopause. The late reproductive years are characterized by regular menses associated with elevated FSH levels. **The menopausal transition is characterized by elevated FSH levels associated with variable cycle lengths and missed menses, whereas the postmenopausal period is marked by amenorrhea. The menopausal transition begins with variability in menstrual cycle length accompanied by rising FSH levels and ends with the final menstrual period. Menopause is defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhea. Postmenopause describes the period following the final menses (3).**

The pathophysiologic consequences of menopause may be best understood by considering that the ovary is a woman's only source of oocytes, her primary source of estrogen and progesterone, and a major source of androgens. Menopause results in infertility secondary to oocyte depletion. Ovarian cessation of progesterone production appears to have no clinical consequences except for the increased risk of endometrial proliferation, hyperplasia, and cancer associated with continued endogenous estrogen production or administration of unopposed estrogen therapy in menopausal women. The possible effects of declining androgen concentrations that occur with aging are an area of both controversy and active investigation.

The major consequences of menopause are related primarily to estrogen deficiency. It is very difficult to distinguish the consequences of estrogen deficiency from those of aging, as aging and menopause are inextricably linked. Studying the effects of estrogen deficiency and replacement in young women with ovarian failure or of drugs that suppress estrogen synthesis (such as gonadotropin-releasing hormone antagonists) helps to distinguish between the effects of aging and estrogen deficiency. These models are imperfect, though, and differ from natural menopause in many ways.

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Principal health concerns of menopausal women include vasomotor symptoms, urogenital atrophy, osteoporosis, cardiovascular disease, cancer, cognitive decline, and sexual problems. Options for caring for menopausal women have increased greatly since hormone therapy (HT) was first introduced in the 1960s. With respect to hormone use, there are many choices of hormone type, dose, and method of administration. Not only have new forms of estrogens and progestins been introduced, but novel ways of combining the two hormones are available. In addition to hormones, selective estrogen receptor modulators (SERMs) and bisphosphonates are available for treatment. Women are requesting more information on complementary and alternative therapies, which are being studied more carefully. The many options now available make caring for postmenopausal women more rewarding as well as more challenging.

Health Concerns After Menopause

Vasomotor Symptoms

Vasomotor symptoms affect up to 75% of perimenopausal women. Symptoms last for 1 to 2 years after menopause in most women, but may continue for up to 10 years or

longer in others. Hot flashes are the primary reason women seek care at menopause and request HT. Hot flashes not only disturb women at work and interrupt daily activities but also disrupt sleep (4). Many women report difficulty concentrating and emotional lability during the menopausal transition. Treatment of vasomotor symptoms should improve these cognitive and mood symptoms if they are secondary to sleep disruption and resulting daytime fatigue. The incidence of thyroid disease increases as women age; therefore, thyroid function tests should be performed if vasomotor symptoms are atypical or resistant to therapy.

The physiologic mechanisms underlying hot flashes are incompletely understood. A central event, probably initiated in the hypothalamus, drives an increased core body temperature, metabolic rate, and skin temperature; this reaction results in peripheral vasodilation and sweating in some women. The central event may be triggered by noradrenergic, serotonergic, or dopaminergic activation. Although an LH surge often occurs at the time of a hot flash, it is not causative, because vasomotor symptoms occur in women who have had their pituitary glands removed. Exactly what role estrogen plays in modulating these events is unknown. Vasomotor symptoms are a consequence of estrogen withdrawal, not simply estrogen deficiency. For example, a young woman with primary ovarian failure resulting from Turner syndrome will have a very high FSH level and low estrogen levels, but she will not experience hot flashes until she is treated with estrogens and then therapy is withdrawn.

Systemic estrogen therapy is the most effective treatment available for vasomotor symptoms and associated sleep disturbance. Although standard doses are usually effective, younger women and those with recent oophorectomy may need higher doses. Healthy women in the perimenopausal transition who are experiencing bothersome hot flashes but still menstruating may benefit from oral contraceptives. The high doses of estrogens and progestins in oral contraceptives not only effectively treat vasomotor symptoms but also provide cycle control. Very-low-dose estrogen therapy also effectively treats hot flashes for many women. Low-dose oral esterified and conjugated estrogens (0.3 mg daily) (5,6) or transdermal estradiol (0.025 mg weekly) (7) often is effective and is associated with minimal side effects and endometrial stimulation. Progestin therapy must be given concurrently if a woman has not had a hysterectomy, although with low-dose estrogen therapy, intermittent progestin treatment may be an option.

Given the known risks, described in detail later in this chapter, HT should be used at the lowest effective dose for the shortest amount of time that meets treatment goals. The majority of women with very bothersome hot flashes at the time of the menopausal

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transition will benefit from short-term therapy and be able to wean off hormones after several years of use. A major risk of HT, breast cancer, does not appear to increase until after 4 to 5 years of use.

Because vasomotor symptoms appear to be the result of estrogen withdrawal, rather than simply low estrogen levels, if cessation of estrogen therapy is desired, the dose should be reduced slowly over several months. Abruptly stopping treatment may result in a return of disruptive vasomotor symptoms. This recommendation is based on clinical experience, as no controlled trials have been performed to examine the optimal way to cease HT use.

One possible approach to stopping therapy is to reduce the dose and dosing interval slowly, and to let the patient's symptoms guide the pace at which she discontinues

therapy. For example, initially, the patient would be prescribed a reduced dose of HT every day for 2 to 3 months. She would then take the reduced dose every other day for 2 to 3 months, then every third day for 2 to 3 months, and then stop if she is doing well.

When a woman chooses not to take estrogen or when it is contraindicated, other options are available (Table 32.1) (8). Progestin therapy alone is an option for some women.

Medroxyprogesterone acetate (MPA) (Provera) (20 mg/day) and *megestrol acetate (Megace)* (20 mg 2 times daily) effectively treat vasomotor symptoms (9). Several drugs that alter central neurotransmitter pathways also are effective. Agents that decrease central noradrenergic tone, such as *clonidine (Catapres)*, relieve hot flashes, whereas *yohimbine*, an agent that increases noradrenergic tone, exacerbates symptoms (10). *Clonidine* has been shown in randomized, placebo-controlled trials to significantly reduce vasomotor symptoms (11). It may be used orally (0.1–0.2 mg/day) or as a weekly transdermal patch (0.1 mg/day). Potential side effects include orthostatic hypotension and drowsiness.

Table 32.1 Options for the Treatment of Vasomotor Symptoms
<i>Hormone therapy</i>
•Estrogen therapy
•Combination estrogen/progestin therapy
•Progestin therapy
<i>Nonhormonal prescription medications</i>
•Clonidine
•Selective serotonin and norepinephrine reuptake inhibitors
•Gabapentin
<i>Nonprescription medications</i>
•Isoflavone supplements
•Soy products
•Black cohosh
•Vitamin E
<i>Lifestyle changes</i>
•Reducing body temperature
•Maintaining a healthy weight
•Smoking cessation
•Paced respiration

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Selective serotonin reuptake inhibitors (SSRIs) also are effective in relieving hot flashes. In a double-blind, randomized, placebo-controlled trial of *paroxetine CR (Paxil)* (12.5 and 25 mg/day), menopausal women with hot flashes experienced a significant reduction in both the frequency and severity of episodes (12). Hot flash composite scores decreased 62% in the *paroxetine* group versus 38% in the placebo group. Actual hot flash frequency decreased by 3.3 hot flashes per day with *paroxetine* versus 1.8 on placebo. The improvement in vasomotor symptoms was independent of any significant change in mood or

anxiety symptoms. Both doses were effective, but the lower dose was better tolerated. The most common side effects were headache, nausea, and insomnia. A modest improvement in symptoms also occurred in a randomized, double-blind, placebo-controlled, crossover trial of *fluoxetine* (*Prozac*) (20 mg/day) (13). Not all studies show an improvement in vasomotor symptoms with SSRIs. In a 9-month, double-blind, parallel-group trial, there was no significant improvement in hot flashes with either *fluoxetine* or *citalopram* (*Celexa*) (10–30 mg/day) compared with placebo (14).

Modulation of other central neurotransmitters with different antidepressants also may be effective, but have greater potential for adverse effects. *Venlafaxine* (*Effexor*) (75 mg/day), a serotonin and norepinephrine reuptake inhibitor, significantly reduced hot flashes in a controlled trial (15). Hot flash scores decreased 61% in the *venlafaxine* group compared with 27% in the placebo group. The active treatment group experienced significantly more side effects, including dry mouth, nausea, and anorexia. A dopamine antagonist, *verapride* (*Agreal*) (100 mg/day), significantly reduced hot flashes in a controlled trial, but side effects of this class of agent include somnolence, hyperprolactinemia, galactorrhea, and tardive dyskinesia.

Gabapentin (*Neurontin*), a gamma-aminobutyric acid analogue approved for the treatment of seizures, also reduced hot flash frequency and severity significantly more than placebo in a double-blind, randomized trial (16). Hot flash scores decreased 54% in the women treated with *gabapentin* (900 mg/day) compared with a 31% reduction in placebo-treated women. The most common adverse events were somnolence, dizziness, and rash.

Bellergal, a combination of *ergotamine*, *phenobarbital*, and *belladonna alkaloids* approved for the treatment of migraines, also reduces hot flashes (17). Its use, though, is limited by anticholinergic side effects, including dry mouth, constipation, and drowsiness.

Many menopausal women are interested in trying nutritional and vitamin supplements for relief of hot flashes. Many of these therapies are claimed to relieve hot flashes but rarely are studied in controlled trials (18). Vasomotor symptoms are particularly sensitive to placebo treatments. Several controlled studies demonstrate a reduction in vasomotor symptoms with soy supplementation, whereas others do not. In one randomized study, soy protein (60 g/day) reduced hot flashes by 45%, a significantly greater reduction than the 30% seen in placebo-treated women (19). In another controlled trial, use of *isoflavones* (100 mg/day) significantly decreased vasomotor symptoms when compared with placebo, while also reducing total and low-density lipoprotein cholesterol (20). A large controlled trial of soy protein, with and without isoflavones, demonstrated no effect of isoflavones on vasomotor symptoms (21). Soy-related compounds may act as SERMs, with their effects modulated through interactions with the estrogen receptor.

Although often recommended, *vitamin E* (800 IU/day) only minimally reduced hot flashes in a placebo-controlled, randomized, crossover trial (22). Uncontrolled studies of acupuncture (23), exercise, and paced respiration show an improvement in vasomotor symptoms with the use of these techniques. Women may choose to use alternative and complementary therapies for relief of symptoms, but they should be aware that their safety and efficacy are unproved. Being in a cool environment is associated with fewer subjective

and objective hot flashes (24), so women experiencing symptoms should be encouraged to keep

the room temperature low and wear light, layered clothing. Overweight women and those who smoke have more severe vasomotor symptoms than women of normal weight and nonsmokers. These findings provide additional reasons to encourage women to lose weight and stop smoking (25,26).

Urogenital Atrophy

Urogenital atrophy results in vaginal dryness and pruritus, dyspareunia, dysuria, and urinary urgency. These common problems in menopausal women respond well to therapy.

Systemic estrogen therapy is effective for the relief of vaginal dryness, dyspareunia, and urinary symptoms. For women who should not or choose not to use estrogen therapy, another option is topical application. Because systemic absorption is low, endometrial stimulation is minimal; thus vaginal estrogen therapy may be appropriate even for symptomatic women with breast cancer. Low doses of *estrogen cream (Premarin, Estrace)* (0.5 g) are effective when used only 1 to 3 times weekly (27). An *estradiol vaginal tablet (Vagifem)* (25 µg) inserted twice weekly, which may be less messy and easier to use than estrogen cream, is available. An *estrogen containing vaginal ring (Estring)* (7.5 µg/day), which is placed in the vagina every 3 months and slowly releases a low dose of estradiol, also is available (28).

Studies of the vaginal tablets and ring have confirmed endometrial safety at 1 year, but studies are not available on the long-term effects of low-dose vaginal estrogen therapy on the endometrium. Women using vaginal estrogen therapy should be asked to report any vaginal bleeding, and this bleeding should be evaluated thoroughly. Typically, systemic progestin therapy is not prescribed to women using low-dose vaginal estrogen. In the absence of supportive evidence, it is not unreasonable to recommend the use of progestin for 12 to 14 days, every 6 to 12 months, in women who are long-term users of vaginal estrogens, especially overweight women or those otherwise at increased risk for endometrial hyperplasia. Lubricants (e.g., *Replens, KY Jelly*) are a nonhormonal alternative for reducing discomfort with intercourse in the presence of urogenital atrophy.

Vaginal estrogen therapy appears to reduce urinary symptoms, such as frequency and urgency, and has been shown to reduce the likelihood of recurrent urinary tract infections in postmenopausal women (29). The effect of estrogen therapy on urinary incontinence is unclear. Whereas the results of some studies suggest improvement in incontinence with estrogen therapy, others show a worsening of symptoms (30).

Osteoporosis

Osteoporosis, or low bone mass, affects an estimated 30 million women in the United States, or approximately 55% of women older than age 50 years (31). **Annual expenditures for medical care of osteoporotic fractures in the United States total \$15 billion.** Because therapy is most likely to benefit those at highest risk, it is important to review a woman's risk factors for osteoporosis when making treatment decisions and to consider bone mineral density screening for high-risk women (Table 32.2). Nonmodifiable risk factors include age, Asian or Caucasian race, family history, small body frame, history of a prior fracture, early menopause, and prior oophorectomy. Modifiable risk factors include decreased intake of calcium and vitamin D, smoking, and a sedentary lifestyle. Medical conditions associated with an increased

risk of osteoporosis include anovulation during the reproductive years (eg, secondary to excess exercise or an eating disorder), hyperthyroidism, hyperparathyroidism, chronic renal disease, and diseases requiring systemic corticosteroid use.

Table 32.2 Risk Factors for Osteoporosis
<i>Nonmodifiable</i>
•Age
•Race (Caucasian, Asian)
•Small body frame
•Early menopause
•Prior fracture
•Family history of osteoporosis
<i>Modifiable</i>
•Inadequate intake of calcium and vitamin D
•Smoking
•Low body weight
•Excess alcohol use
•Sedentary lifestyle
<i>Associated Medical Conditions</i>
•Hyperthyroidism
•Hyperparathyroidism
•Chronic renal disease
•Conditions requiring systemic corticosteroid use

Bone mineral density (BMD) measurements may be used to diagnose osteoporosis, determine fracture risk, and identify women who would benefit from therapeutic interventions. **Dual x-ray absorptiometry (DXA) of the hip and spine is the primary technique for BMD assessment. BMD is expressed as a T-score, which is the number of standard deviations from the mean for a young, healthy woman. A T-score above -1 is considered normal, a value between -1 and -2.5 denotes osteopenia, and a score below -2.5 indicates osteoporosis.** Although there is a strong association between BMD and fracture risk, a woman's age, overall health status, and risk for falls also influence her fracture risk.

Evaluation of BMD by DXA is recommended for all women aged 65 and older, regardless of risk factors, and for younger postmenopausal women with 1 or more risk factors, other than being white and menopausal (32). Osteoporosis may be assumed in any menopausal woman with a low-impact trauma fracture.

Counseling women to alter modifiable risk factors is important for both the prevention and treatment of osteoporosis. Many women have diets deficient in calcium and vitamin D and will benefit from dietary changes and supplementation. Women should receive 1,000 to 1,500 mg of calcium and 400 to 800 IU of vitamin D daily. This may be achieved through diet or vitamin and mineral supplementation. Reducing the risk of osteoporosis is another

of the many health benefits of smoking cessation and regular exercise. Treatment is indicated for all women with osteoporosis as well as for those with osteopenia and additional risk factors. Drug therapies for the prevention and treatment of osteoporosis are principally antiresorptive drugs that reduce bone loss and anabolic agents that stimulate new bone formation (Table 32.3).

Hormone therapy is effective in preventing and treating osteoporosis. In observational studies, estrogen therapy has been shown to reduce osteoporosis-related fractures by

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approximately 50% when started soon after menopause and continued long term. It also significantly decreases fracture rates in women with established disease (33). **The Women's Health Initiative (WHI) randomized controlled trial confirmed a significant (34%) reduction in hip fractures in healthy women receiving HT (conjugated equine estrogen 0.625 mg with MPA 5 mg; PremPro) after a mean follow-up of 5 years (34) (Table 32.4).** Recent studies demonstrate that even very-low-dose estrogen therapy (*estradiol* 0.25 mg/day; *conjugated equine estrogen* 0.3 mg/day with *MPA* 1.5 mg/day, [*PremPro*]; *transdermal estradiol* 0.025 mg/day [*Climara, Vivelle, Alora*]; and 0.014 mg/day [*Menostar*]), combined with calcium and vitamin D, produce significant increases in bone mineral density compared with placebo (35,36,37).

Table 32.3 Options for Osteoporosis Prevention and Treatment

Bisphosphonates

Fosamax (Alendronate) (35–70 mg/week)

Actonel (Risedronate) (35 mg/week)

Boniva (Ibandronate) (150 mg/month)

- Additional potential benefits: none
- Potential risks: esophageal ulcers
- Side effects: gastrointestinal distress, arthralgias/myalgias

Hormone Therapy

Estrogen or Estrogen/Progestin Therapy

- Additional potential benefits: treatment of vasomotor symptoms and urogenital atrophy
- Potential risks: breast cancer, gallbladder disease, venous thromboembolic events, cardiovascular disease, stroke
- Side effects: vaginal bleeding, breast tenderness

Selective Estrogen Receptor Modulators (SERMS)

Evista (Raloxifene) (60 mg/day)

- Additional potential benefits: reduced risk of breast cancer
- Potential risks: venous thromboembolic events
- Side effects: vasomotor symptoms, leg cramps

Other

Calcitonin (Miacalcin) (200 IU /day intranasally or 100 IU/day subcutaneously or intramuscularly)

- Additional potential benefits: none

- Potential risks: none

- Side effects: rhinitis, back pain

Forteo (Teriparatide) (20 µg/day subcutaneously)

- Additional potential benefits: none

- Potential risks: osteosarcoma after long-term use in rodents, hypercalcemia

- Side effects: leg cramps

Bisphosphonates, including *alendronate* (Fosamax, 35–70 mg weekly), *risedronate* (Actonel, 35 mg weekly), and *ibandronate* (Boniva, 150 mg monthly) specifically inhibit bone resorption and are very effective for both osteoporosis prevention and

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treatment (38,39). Patients should be instructed to take these drugs on an empty stomach with a large glass of water and then to remain upright for at least 30 to 60 minutes. The major side effect is gastrointestinal distress; esophageal ulceration is a rare occurrence. Once-weekly administration of high-dose *alendronate* or *risedronate* is therapeutically equivalent to daily dosing and more convenient for patients. Monthly dosing with *ibandronate* is very convenient and may result in improved long-term continuance with bisphosphonate therapy.

Table 32.4 Summary of Women's Health Initiative Study Results	
Risks per 10,000 Person-Years Attributable to Estrogen Plus Progestin^a	
	Per 10,000 Person-Years
Excess Risk	Additional Cases
Coronary heart disease	7
Stroke	8
Pulmonary embolism	8
Invasive breast cancer	8
Dementia (WHIMS) (<i>subset older than age 65</i>)	23
Reduced Risk	Fewer Cases
Hip fracture	5
Colorectal cancer	6
Risks per 10,000 Person-Years Attributable to Estrogen Alone (Hysterectomized Women)^b	
	Per 10,000 Person-Years
Excess Risk	Additional Cases
Stroke	12
Deep venous thrombosis	6
Reduced Risk	Fewer Cases
Hip fracture	6
No Difference	
Coronary heart disease	
Invasive breast cancer	

Colorectal cancer

WHIMS, Women's Health Initiative Memory Study.

^a From **Writing Group for the Women's Health Initiative Investigators**. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–333; and **Shumaker S, Legault C, Rapp S, et al**. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. *JAMA* 2003; 289: 2651–2662.

^b From **Women's Health Initiative Steering Committee**. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA* 2004; 291: 1701–1712.

Selective estrogen receptor modulators are compounds that act as both estrogen agonists and antagonists, depending on the tissue. Raloxifene (Evista, 60 mg) is a SERM that has been approved for both the prevention and treatment of osteoporosis (40).

Raloxifene exercises estrogenlike actions on bone and lipids without stimulating the breast or endometrium (41). *Calcitonin* nasal spray (*Miacalcin*, 200 IU) is another approved treatment for established osteoporosis. Parathyroid hormone (human recombinant PTH 1-34) (*teriparatide*, *Forteo*, 20 µg subcutaneously) is a novel therapy for osteoporosis. Unlike most

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treatments for osteoporosis that inhibit bone resorption, parathyroid hormone stimulates new bone formation. Treatment of postmenopausal osteoporotic women with parathyroid hormone by daily subcutaneous injection results in dramatic increases in vertebral, femoral, and total body bone mineral density, and significant reductions in vertebral and nonvertebral fractures (42). Parathyroid hormone is indicated for postmenopausal women with osteoporosis who are at very high risk for fracture.

Cardiovascular Disease

Cardiovascular disease is the leading cause of death for women, accounting for approximately 45% of mortality. Nonmodifiable risk factors include age and family history. Modifiable risk factors include smoking, obesity, and a sedentary lifestyle. Medical conditions associated with an increased risk of heart disease include diabetes, hypertension, and hypercholesterolemia.

Advising women to alter modifiable risk factors and adequately treating diabetes, hypertension, and hypercholesterolemia are important measures in reducing the risk of heart disease. In the past, prevention of heart disease was thought to be a potential benefit of HT. Epidemiologic studies report an approximately 50% decrease in heart disease in woman who use HT (43,44). This observed reduction in coronary heart disease was thought secondary to beneficial effects of HT on lipid levels (45) and direct actions on the vascular wall. Observational studies are prone to bias, though, and woman who choose to use hormones are generally at lower risk for heart disease than those who do not (46).

The WHI randomized controlled trial of combination HT versus placebo showed that not only does HT not prevent heart disease in healthy women, it actually increases the risk of cardiovascular events (34). The WHI is a 15-year study sponsored by the National Institutes

of Health that examines ways to prevent heart disease, osteoporosis, and breast and colorectal cancer in women. There are several different studies in WHI involving more than 160,000 healthy postmenopausal women. The WHI randomized controlled trial enrolled approximately 16,000 women nationwide between the ages of 50 and 79 years. The average age of women in the study was 63 years. The major goal of the WHI clinical trial was to determine whether combined estrogen and progestin HT prevented heart disease and fractures, and whether there were risks associated with HT use. **After an average of 5 years of follow-up, heart disease and stroke were significantly increased in HT users by 29% and 41%, respectively.**

Approximately 11,000 women without a uterus participated in a separate WHI study and were randomized either to estrogen alone or placebo. After an average follow-up of 7 years, there was no increased risk of heart disease in estrogen users (47). Estrogen use did have adverse vascular effects, however, increasing the risk of stroke by 39% and venous thromboembolism by 33%.

There appears to be no role for HT in the prevention of cardiovascular disease, not only in healthy women, but also in women with established heart disease. The Heart and Estrogen/Progestin Replacement Study (HERS), a randomized, placebo-controlled trial of combination estrogen–progestin therapy for secondary prevention of heart disease, also did not demonstrate any reduction in cardiovascular events (48). Overall, there were no significant differences in cardiovascular outcomes between HT and placebo-treated women. There was a significant time factor, however, with more cardiovascular events occurring in women using HT in year 1, and fewer in years 4 and 5.

The WHI trials and the HERS study examined only treatment with *conjugated equine estrogens* and *medroxyprogesterone acetate*. The effects of other oral estrogen agents, transdermal estradiol, cyclic HT, or therapy with other progestins may be different. In

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addition, the average age of women participating in these trials was more than 15 years beyond the age at which women typically initiate HT for the treatment of vasomotor symptoms. It is possible that early initiation of HT may result in a more favorable risk-benefit profile. In the absence of data from randomized controlled trials, the conservative approach is to assume that the risks of various HT regimens are similar.

Selective estrogen receptor modulators, such as *raloxifene*, also improve the lipid profile, decreasing total and low-density lipoprotein cholesterol similarly to oral HT, but without increasing high-density lipoprotein cholesterol or triglycerides (49). Whether the beneficial effects of *raloxifene* on lipid levels will translate into a reduced incidence of heart disease currently is being studied in the Raloxifene Use for the Heart (RUTH) trial, a large randomized, placebo-controlled study examining the effects of *raloxifene* on cardiovascular disease. In a secondary analysis of **results from a randomized, controlled trial of *raloxifene* versus placebo in more than 7,000 women with osteoporosis, there were no significant differences between groups with regard to coronary and cerebrovascular events. Among a subset of approximately 1,000 women with increased cardiovascular risk at baseline, the women who received *raloxifene* experienced a significant 40% reduction in cardiovascular events (50).**

Breast Cancer

Breast cancer is the most common cancer in women, is the second leading cause of cancer death, and is a major health concern for menopausal women (51). For women in the United States, the lifetime risk of developing invasive breast cancer is 12%; therefore, any therapies that reduce or increase this risk will have a major impact on women's health. Risk factors for breast cancer include age, early menarche, late menopause, family history, and prior breast disease, including epithelial atypia and cancer. Oophorectomy and term pregnancy before the age of 30 are associated with reduced risk. Many of these risk factors are consistent with the hypothesis that prolonged estrogen exposure increases the risk of breast cancer.

Long-term use of HT is associated with an increased risk of breast cancer (52).

Observational studies show a relative risk of approximately 1.3 with long-term HT use, generally defined as greater than 5 years. The results of several studies suggest that the risk of breast cancer associated with the use of estrogen alone may be lower, with a higher risk in users of estrogen plus progestin (53,54). The WHI randomized controlled trial demonstrated a significant (26%) increase in the risk of invasive breast cancer after approximately 5 years of use of HT (34). In women with a prior hysterectomy, there was no increased risk of breast cancer after an average of 7 years of estrogen use alone (47).

The SERM *tamoxifen* (Nolvadex) is an estrogen antagonist in the breast that is used in the treatment of estrogen-receptor positive breast cancer. *Tamoxifen* (20 mg) also has been approved for the prevention of breast cancer in high-risk women, resulting in an approximately 50% reduction in the risk of disease (55). *Raloxifene* also may reduce the risk of breast cancer. Postmenopausal women receiving *raloxifene* as part of a large osteoporosis treatment trial experienced a 76% reduction in the risk of invasive breast cancer compared with placebo-treated women (56). The Study of Tamoxifen and Raloxifene (STAR) trial is comparing the effectiveness of *raloxifene* and *tamoxifen* for the prevention of breast cancer in high-risk women. The Continuing Outcomes Relevant to Evista (CORE) trial is evaluating the effect of *raloxifene* on breast cancer risk in women with osteoporosis.

The risk of venous thromboembolism (VTE) is increased approximately threefold with the use of *tamoxifen* and *raloxifene*. This increase is similar to the increased risk that occurs in HT users. Hot flashes are increased with *raloxifene* and *tamoxifen* use, and *raloxifene* is associated with leg cramps. *Tamoxifen* acts as an estrogen agonist in the

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endometrium, increasing the risk of endometrial polyps, hyperplasia, and cancer, whereas no endometrial stimulation is seen with *raloxifene*.

Performing a screening mammography examination annually for women older than age 50 years reduces breast cancer mortality. Monthly breast self-examination also is recommended. Women at increased risk for breast cancer are advised not to use HT, or to use it only short term. Women at high risk also may elect to take *tamoxifen* therapy.

Alzheimer Disease

Alzheimer disease is the most common form of dementia. Women are at greater risk for developing the disease than men, and the number of affected individuals in the United States is expected to double to more than 8 million by 2010. Several small trials and observational studies have suggested that hormone therapy use may decrease the risk of

Alzheimer disease (57). A randomized, controlled study in women with mild to moderate Alzheimer disease, however, showed that 1 year of estrogen treatment neither slowed disease progression nor improved cognition (58). The effect of HT on cognitive function in women without dementia was studied in the WHI Memory Study (WHIMS), a randomized, double-blind, placebo-controlled trial of women aged 65 years or older enrolled in the WHI trial. In contrast to the findings of observational studies, **women randomized to HT in WHIMS experienced a significant twofold increased risk of dementia, most commonly Alzheimer disease** (59). In addition, HT use was associated with an adverse effect on cognition. Compared with placebo-treated women, women in the HT group scored significantly lower on the Modified Mini-Mental State Examination (60). **Given the increased incidence of stroke identified in HT users in the WHI trial, it is possible that small, undetected cerebrovascular events were more likely to occur in the HT group, increasing the risk of dementia.**

Risks of Hormone Therapy

In addition to an increased risk of heart attack, stroke, breast cancer, and Alzheimer disease, VTEs are increased approximately two- to threefold with HT use. This was confirmed in the WHI clinical trial, in which women assigned to HT experienced twice the incidence of deep venous thrombosis and pulmonary embolism than women randomized to placebo (34). Women taking HT should be advised to stop therapy several days before elective surgery or periods of prolonged immobilization. It is possible that transdermal estrogen therapy may not be associated with an increased risk of VTE. In one case-control study, oral but not transdermal estrogen therapy was associated an increased risk of VTEs (61). There also is a twofold risk of gallbladder disease with HT use. Common side effects include breast tenderness, exacerbation of migraine headaches, and vaginal bleeding.

Contraindications to HT use include known or suspected breast or endometrial cancer, undiagnosed abnormal genital bleeding, active thromboembolic disorders, and active liver or gallbladder disease. Relative contraindications include heart disease; migraine headaches; and a history of liver or gallbladder disease, endometrial cancer, or thromboembolic events. These situations require a thoughtful assessment of potential risks and benefits and documentation of informed patient consent before treatment.

The use of unopposed estrogen is associated with an increased risk of endometrial hyperplasia and cancer. Therefore, combination *estrogen-progestin* therapy is recommended for all women with a uterus. Treatment may be provided in a sequential manner, with *estrogen* daily and *progestin* for 12 to 14 days of each month, or in a continuous-combined fashion with *estrogen* and a lower dose of *progestin* daily.

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Sequential regimens result in regular, predictable vaginal bleeding. The benefit of continuous-combined regimens is that approximately 60% to 70% of women will experience amenorrhea by the end of 1 year of therapy; the problem is that the bleeding that does occur is irregular and unpredictable (62). Several new combination therapies have been approved for use that combine *norethindrone acetate* (*NETA*) as the progestin, with either *ethinyl estradiol* (*FemHRT*) or *estradiol* (*Activella*). These products, as well as the low-dose *PremPro* formulations (0.45/1.5, 0.3/1.5 mg/day), have a lower incidence of breakthrough

bleeding than other continuous-combined regimens. In general, older women and women who have been menopausal for several years experience less irregular bleeding with continuous-combined regimens than do younger, recently menopausal women.

For women who note symptoms of depressed mood or bloating with *MPA*, oral natural *micronized progesterone* (*Prometrium*, 100–200 mg/day) is approved for use in HT regimens. It results in a more favorable lipid profile and may have different side effects (45). The major adverse effect of oral progesterone appears to be drowsiness, which may be a benefit for some women if taken at bedtime. *Micronized progesterone* contains peanut oil and should not be used by women with peanut allergies. Other options for women with intolerance to progestin therapy include using cyclic progestins only 3 to 4 times per year, rather than 12 to 14 days of each month. A progestin-containing intrauterine device or vaginal progesterone cream also may be used. When utilizing an unapproved progestin regimen, increased surveillance of the endometrium with serial ultrasound monitoring and/or endometrial biopsy is indicated (63). Various formulations used for HT are shown in Table 32.5.

Sexual Dysfunction

Many women experience sexual dysfunction, although the exact incidence and etiology are unknown. Sexual dysfunction may involve decreased interest or desire to initiate activity, as well as decreased arousal or ability to achieve an orgasm during sexual relations. The etiology of sexual dysfunction often is multifactorial, including psychological problems such as depression or anxiety disorders, conflict within the relationship, issues relating to prior physical or sexual abuse, medication use, or physical problems that make sexual activity uncomfortable, such as endometriosis or atrophic vaginitis. Analyzing data from the National Health and Social Life Survey, a probability sample of sexual behavior conducted in 1992 with a cohort of adults, **the prevalence of sexual dysfunction in the United States was estimated to be as high as 43% in women and 31% in men** (64). Although some studies describe decreased levels of sexual desire and activity in older women, sexual concerns are common and not specifically a problem of menopause.

Female sexual dysfunction after menopause is a complex problem with many etiologies. Careful evaluation of physiological, psychological, lifestyle, and relationship variables is required to optimize therapy. Treatment of anxiety and depression, adjustment of antidepressant medication, and relationship counseling may improve sexual function. Specific exercises and activities, often performed under the guidance of a sex therapist, aid many women and couples with sexual dysfunction. Specific treatment of genitourinary atrophy with systemic or local vaginal estrogen therapy or vaginal lubricants effectively reduces dyspareunia and may improve sexual arousal and response. ***Sildenafil citrate (Viagra)* was ineffective in a large randomized, double-blind, placebo-controlled study of women with sexual dysfunction** (65). A clitoral therapy device (*EROS-CTD™*) approved by the U.S. Food and Drug Administration may increase clitoral blood flow and improve arousal in some women (66).

Androgen therapy may have a role in the treatment of sexual dysfunction in menopausal women who have low androgen levels and no other identifiable cause

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for their sexual problem (67). Although ovarian and adrenal androgen levels decline with age,

there is not an abrupt decrease in the production of these hormones at menopause as that which occurs with ovarian estradiol (68). Surgical menopause is an exception; **testosterone levels decrease by approximately 50% following bilateral oophorectomy.**

In a double-blind, crossover study of surgically menopausal women, the administration of supraphysiologic doses of intramuscular *testosterone* resulted in significantly higher scores of sexual desire, fantasy, and arousal than did treatment with estradiol alone or placebo (69). In a double-blind, randomized study of the effects on libido of oral *methyltestosterone* (1.25 mg/day) combined with *esterified estrogens* (0.625 mg/day, *Estratest HS*), women randomized to treatment with the estrogen-androgen combination reported significantly improved sexual interest and desire compared with women treated with estrogen alone (70). In randomized, double-blind, placebo-controlled studies of estrogen-treated women without ovaries who had sexual dysfunction, physiologic testosterone therapy administered by a transdermal patch resulted in significant increases in sexual activity and pleasure (71,72).

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A popular, but untested treatment is the use of a small amount of *testosterone ointment* or *cream* (1%), compounded at many pharmacies, applied topically to the vagina, arms, or low abdomen.

Table 32.5 Hormone Therapy Options^a

Table 32.5 Hormone Therapy Options^a			
Oral Estrogen Products			
Composition	Product Name	Dose (mg/day)	
Conjugated equine estrogens	<i>Premarin</i>	0.3, 0.45, 0.625, 0.9, 1.25	
Synthetic conjugated estrogens	<i>Cenestin</i>	0.3, 0.45, 0.625, 0.9, 1.25	
Esterified estrogens	<i>Menest</i>	0.3, 0.625, 1.25, 2.5	
17β-estradiol	<i>Estrace, generics</i>	0.5, 1.0, 2.0	
Estrone (estropipate)	<i>Ortho-Est, Ogen, generics</i>	0.625, 1.25	
Transdermal/Topical Estrogen Products			
Composition	Product Name	Release Rate (mg/day)	Dose
17β-estradiol matrix patch	<i>Alora</i>	0.025, 0.05, 0.075, 0.1	Twice weekly
	<i>Climara</i>	0.025, 0.0375, 0.05, 0.075, 0.1	Once weekly
	<i>Esclim</i>	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	<i>Menostar</i>	0.014	Once weekly

	<i>Vivelle (Dot)</i>	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
17β-estradiol reservoir patch	<i>Estraderm</i>	0.025, 0.05, 0.1	Twice weekly
17β-estradiol	<i>Estrogel</i>	0.035	Daily application via metered-dose pump
17β-estradiol	<i>Estrasorb</i>	0.05	Daily application of 2 packets
Vaginal Estrogen Products			
Composition	Product Name	Recommended Dose	
Vaginal Creams			
17β-estradiol	<i>Estrace vaginal cream</i>	0.5–1 g, 2–3 times weekly	
Conjugated equine estrogens	<i>Premarin vaginal cream</i>	0.5–1 g, 2–3 times weekly	
Vaginal Rings			
17β-estradiol	<i>Estring</i>	Device releases 7.5 μ g/day for 90 days	
Estradiol acetate	<i>Femring</i>	Device releases 5 or 10 μ g/day for 90 days (systemic estradiol levels achieved)	
Vaginal Tablet			
Estradiol hemihydrate	<i>Vagifem</i>	1 tablet (25 μ g) twice weekly	
Progestogens			
Composition	Product Name	Dose	
Progestin: Oral Tablet			
Medroxyprogesterone acetate	<i>Provera, generics</i>	2.5, 5, 10 mg	
Norethindrone	<i>Micronor, Nor-QD, generics</i>	0.35 mg	
Norethindrone acetate	<i>Aygestin, generics</i>	5 mg	
Megestrol acetate	<i>Megace</i>	20, 40 mg	
Progestin: Intrauterine System			
Levonorgestrel IUS	<i>Mirena</i>	20 μ g/day release rate (5-year use)	
Progesterone: Oral Capsule			
Micronized progesterone USP	<i>Prometrium</i>	100, 200 mg	
Progesterone: Vaginal Gel			

Progesterone	<i>Prochieve 4%</i>	45 mg/applicator
Combination Estrogen-Progestogen Products		
Composition	Product Name	Dose (per day)
Oral Continuous-Cyclic Regimen		
Conjugated equine estrogens (E)	<i>Premphase</i>	0.625 mg E + 5.0 mg P
+medroxyprogesterone acetate (P)		(E alone days 1–14, E +P days 15–28)
Oral Continuous-Combined Regimen		
Conjugated equine estrogens (E)	<i>Prempro</i>	0.625 mg E + 2.5 or 5.0 mg P
+medroxyprogesterone acetate (P)		0.3 or 0.45 mg E + 1.5 mg P
Ethinyl estradiol (E)	<i>Femhrt</i>	5 µg E + 1 mg P
+norethindrone acetate (P)		
17β-estradiol (E)	<i>Activella</i>	1 mg E + 0.5 mg P
+norethindrone acetate (P)		
Oral Intermittent-Combined Regimen		
17β-estradiol (E)	<i>Ortho-Prefest</i>	1 mg E + 0.09 mg P
+norgestimate (P)		(E alone for 3 days, followed by E +P for 3 days)
Transdermal Continuous-Combined Regimen		
17β-estradiol (E)	<i>CombiPatch</i>	0.05 mg E + 0.14 or 0.25 mg P
+norethindrone acetate (P)		Twice weekly
17β-estradiol (E)	<i>Climara Pro</i>	0.045 mg E + 0.0015 mg P
+ levonorgestrel (P)		Once weekly
^a Table modified from North American Menopause Society . <i>Menopause practice: a clinician's guide</i> . Cleveland, OH: North American Menopause Society, 2004. Used with permission.		

Potential risks of androgen therapy include hirsutism, acne, irreversible deepening of the voice, and adverse changes in liver function and lipid levels. As most androgens are aromatized to estrogens, androgen therapy may pose the same risks as estrogen therapy. Women who elect a trial of therapy should be informed of the potential risks, unproven efficacy, and off-label nature of use.

Summary

There are many options available to address the quality of life and health concerns of menopausal

women. Currently, the primary indication for HT is the alleviation of hot flashes and associated symptoms. Further details regarding these recommendations have been published by the American College of Obstetricians and Gynecologists and the North American Menopause Society (73,74). **Women must be informed of the potential benefits and risks of all therapeutic options, and care should be individualized based on a woman's medical history, needs, and preferences.**

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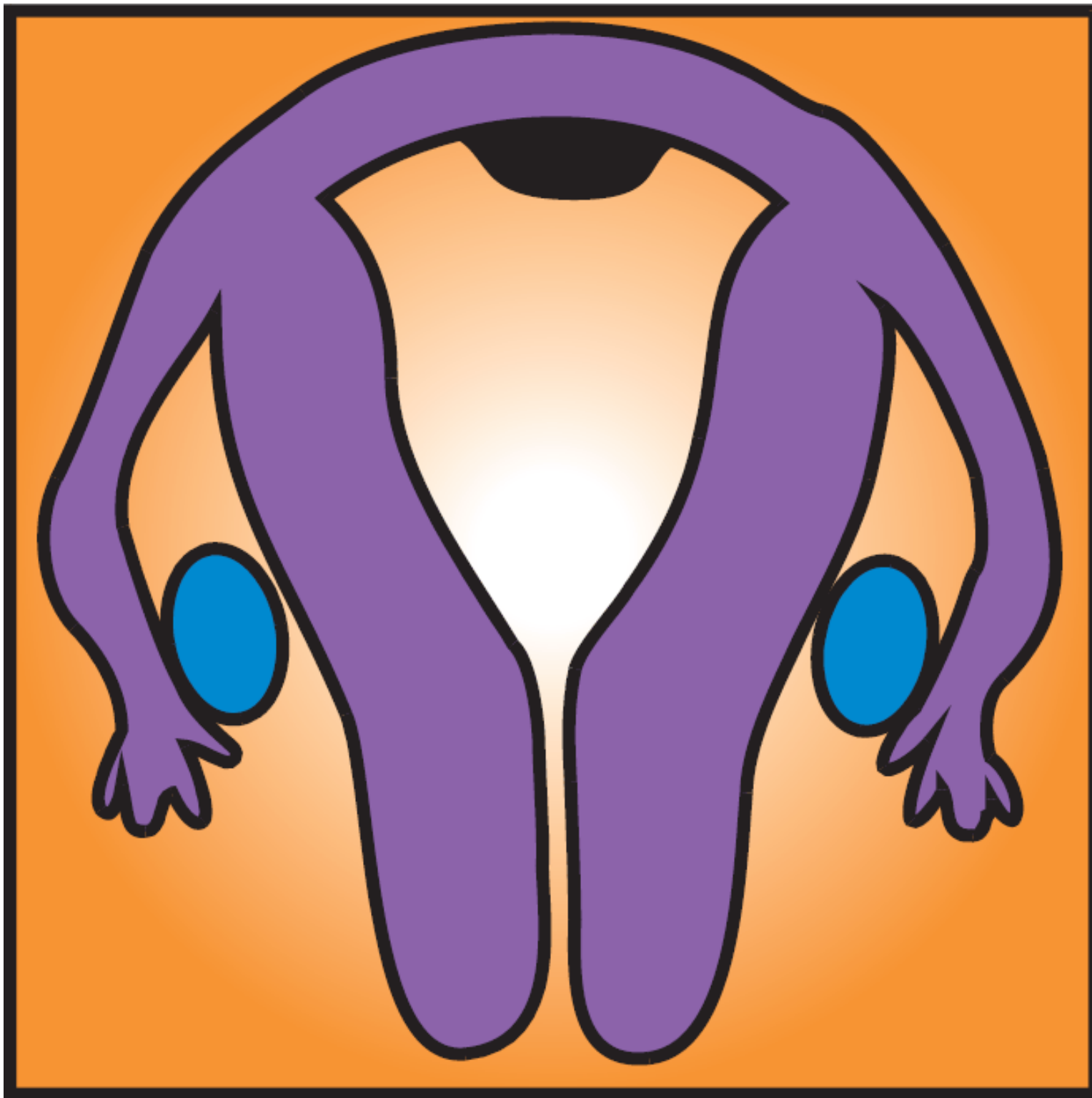
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33

Uterine Cancer

John R. Lurain



- **Most risk factors for the development of endometrial carcinoma are related to prolonged, unopposed estrogen stimulation.**
- **Office endometrial aspiration biopsy is the accepted first step in evaluating a woman with abnormal uterine bleeding or suspected endometrial pathology.**
- **Papillary serous and clear cell endometrial carcinomas make up less than 10% of endometrial cancers, yet account for more than one half of all endometrial cancer deaths.**
- **Most patients with endometrial cancer should undergo surgical staging, including abdominal exploration, peritoneal cytology, hysterectomy, bilateral salpingo-oophorectomy, and selective pelvic and para-aortic lymphadenectomies.**
- **The most important adverse prognostic variables in endometrial cancer are advancing patient age, nonendometrioid or grade 3 histology, deep myometrial invasion, lymph-ovascular space invasion, large tumor size, cervix extension, lymph node metastasis, and intraperitoneal spread.**
- **Postoperative adjuvant radiotherapy in selected patients with endometrial cancer decreases the risk of local vaginal/pelvic recurrence and improves disease-free survival.**
- **Overall 5-year survival rate in endometrial cancer is approximately 75%.**
- **Uterine sarcomas are, in general, the most malignant group of uterine tumors and differ from endometrial cancers with regard to diagnosis, clinical behavior, pattern of spread, and management.**

Endometrial carcinoma is the most common malignancy of the female genital tract, accounting for almost one half of all gynecologic cancers in the United States.

In 2006, an estimated 41,200 new cases and 7,350 cancer-related deaths are anticipated. Endometrial carcinoma is the fourth most common cancer, ranking behind breast, lung, and bowel cancers, and the eighth leading cause of death from malignancy in women. Overall, about 2% to 3% of women develop endometrial cancer during their lifetime (1).

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In recent years, certain factors have led to an increasing awareness of and emphasis on diagnosis and treatment of endometrial cancer. These factors include the declining incidence of cervical cancer and related deaths in the United States, prolonged life expectancy, postmenopausal use of hormone therapy, and earlier diagnosis. The availability of easily applied diagnostic tools and a clearer understanding of premalignant lesions of the endometrium have led to an increase in the number of women diagnosed with endometrial cancer. Although endometrial carcinoma usually presents as early-stage disease and can generally be managed without radical surgery or radiotherapy, deaths from endometrial carcinoma now exceed those from cervical carcinoma in the United States. **Endometrial cancer is a disease that occurs primarily in postmenopausal women and is increasingly virulent with advancing age. The role of estrogen in the development of most endometrial cancers has clearly been established. Any factor that increases exposure to unopposed estrogen increases the risk for endometrial cancer.**

During the past several decades, the histopathology, spread patterns, and clinicopathologic factors that affect the prognosis of endometrial cancers have been better defined. Management of endometrial cancer has evolved from a program of preoperative intrauterine or external pelvic irradiation followed by hysterectomy based on clinical staging, to an individualized approach using hysterectomy as primary therapy and employing additional postoperative treatment depending on surgical and pathologic findings. Further analysis and investigation are needed to determine whether this initial operative approach to treatment and staging, followed by targeted postoperative therapy, will translate into improved survival rates and lower morbidity.

Epidemiology and Risk Factors

There appear to be two different pathogenetic types of endometrial cancer (2). **Type I, accounting for about 75% to 85% of cases, occurs in younger, perimenopausal women with a history of exposure to unopposed estrogen, either endogenous or exogenous.** In these women, tumors begin as hyperplastic endometrium and progress to carcinoma. These "estrogen-dependent" tumors tend to be better differentiated and have a more favorable prognosis than tumors that are not associated with hyperestrogenism. **Type II endometrial carcinoma occurs in women with no source of estrogen stimulation of the endometrium.** These spontaneously occurring cancers are not associated pathologically with endometrial hyperplasia, but may arise in a background of atrophic endometrium. They are less differentiated and associated with a poorer prognosis than estrogen-dependent tumors. These "estrogen-independent" tumors tend to occur in older, postmenopausal, thin women and are present disproportionately in African-American and Asian women. Over the past decade, molecular genetic studies have shown that these two tumor types evolve via distinct pathogenetic pathways (3). **The most frequent early molecular genetic alterations in type I tumors are mutations in the *PTEN* tumor suppressive gene and *K-ras* oncogene and microsatellite instability. Type II tumors are more often associated with *p53* mutations.**

Several risk factors for the development of endometrial cancer have been identified (4,5,6,7,8,9) (Table 33.1). **Most of these risk factors are related to prolonged, unopposed estrogen stimulation of the endometrium.** Nulliparous women have 2 to 3 times the risk of parous women. Infertility and a history of irregular menses as a result of anovulatory cycles (prolonged exposure to estrogen without sufficient progesterone) increase the risk. Natural menopause occurring after age 52 years increases the risk for endometrial cancer 2.4 times compared with women who experienced menopause before 49 years of age, probably as a result of prolonged exposure of the uterus to progesterone-deficient menstrual cycles. **The risk of endometrial cancer is increased 3 times in women who are 21 to 50 pounds overweight and 10 times in those more than 50 pounds overweight** (resulting from

excess estrone as a result of peripheral conversion of adrenally derived androstenedione by aromatization in fat).

Table 33.1 Risk Factors for Endometrial Cancer

<i>Characteristic</i>	<i>Relative Risk</i>
Nulliparity	2-3
Late menopause	2.4
Obesity	
21-50 lb overweight	3
>50 lb overweight	10
Diabetes mellitus	2.8
Unopposed estrogen therapy	4-8
<i>Tamoxifen</i> therapy	2-3
Atypical endometrial hyperplasia	8-29
HNPCC syndrome	20
HNPCC, hereditary nonpolyposis colorectal cancer.	

Other factors leading to long-term estrogen exposure, such as polycystic ovary syndrome and functioning ovarian tumors, also are associated with an increased risk for endometrial cancer. Menopausal estrogen therapy without progestins increases the risk of endometrial cancer 4 to 8 times. This risk increases with higher doses and with more prolonged use and can be reduced to essentially baseline levels by the addition of progestin (8). It has been noted that the use of the antiestrogen *tamoxifen* for treatment of breast cancer is associated with a two- to threefold increased risk for the development of endometrial cancer, although this finding is confounded by the apparent greater risk of endometrial cancer in women who have breast cancer, with or without treatment with tamoxifen (9,10). Diabetes mellitus increases a women's risk for endometrial cancer by 1.3 to 2.8 times. **Women with hereditary nonpolyposis colorectal cancer syndrome (HNPCC), a cancer susceptibility syndrome with germline mutations in mismatch repair genes *MLH1*, *MSH2*, and *MSH6*, have a 40% to 60% lifetime risk for endometrial as well as colon cancer** (11). Other medical conditions, such as hypertension and hypothyroidism, have been associated with endometrial cancer, but a causal relationship has not been confirmed.

Endometrial Hyperplasia

Endometrial hyperplasia represents a spectrum of morphologic and biologic alterations of the endometrial glands and stroma, ranging from an exaggerated physiologic state to carcinoma

in situ. **Clinically significant hyperplasias usually evolve within a background of proliferative endometrium as a result of protracted estrogen stimulation in the absence of progestin influence.** Endometrial hyperplasias are important clinically because they may cause abnormal bleeding, be associated with estrogen-producing ovarian tumors, result from hormonal therapy, and precede or occur simultaneously with endometrial cancer.

The most recent classification scheme endorsed by the International Society of Gynecological Pathologists is based on architectural and cytologic features as well as long-term studies that reflect the natural history of the lesions (12) (Table 33.2).

<i>Type of Hyperplasia</i>	<i>Progression to Cancer (%)</i>
Simple (cystic without atypia)	1
Complex (adenomatous without atypia)	3
Atypical	
Simple (cystic with atypia)	8
Complex (adenomatous with atypia)	29

From **Kurman RJ, Kaminski PF, Norris HJ**. The behavior of endometrial hyperplasia: a long term study of "untreated" hyperplasia in 170 patients. *Cancer* 1985;56:403-412, with permission.

Architecturally, hyperplasias are either simple or complex; the major differing features are complexity and crowding of the glandular elements. **Simple hyperplasia** is characterized by dilated or cystic glands with round to slightly irregular shapes, an increased glandular-to-stromal ratio without glandular crowding, and no cytologic atypia. **Complex hyperplasia** has architecturally complex (budding and infolding), crowded glands with less intervening stroma without atypia. **Atypical hyperplasia refers to cytologic atypia and can be categorized as simple or complex, depending on the corresponding glandular architecture.** Criteria for cytologic atypia include large nuclei of variable size and shape that have lost polarity, increased nuclear-to-cytoplasmic ratios, prominent nucleoli, and irregularly clumped chromatin with parachromatin clearing (see Fig. 33.1).

The risk of endometrial hyperplasia progressing to carcinoma is related to the presence and severity of cytologic atypia. Kurman and colleagues retrospectively studied endometrial curettings from 170 patients with untreated endometrial hyperplasia followed a mean of 13.4 years (13). They found that **progression to carcinoma occurred in 1% of patients with simple hyperplasia, 3% of patients with complex hyperplasia, 8% of patients with atypical simple hyperplasia, and 29% of patients with atypical complex hyperplasia.** Most of the hyperplasias seemed to remain stable (18%) or regress (74%). The premalignant potential of hyperplasia is influenced by age, underlying ovarian disease, endocrinopathy, obesity, and exogenous hormone exposure (14,15).

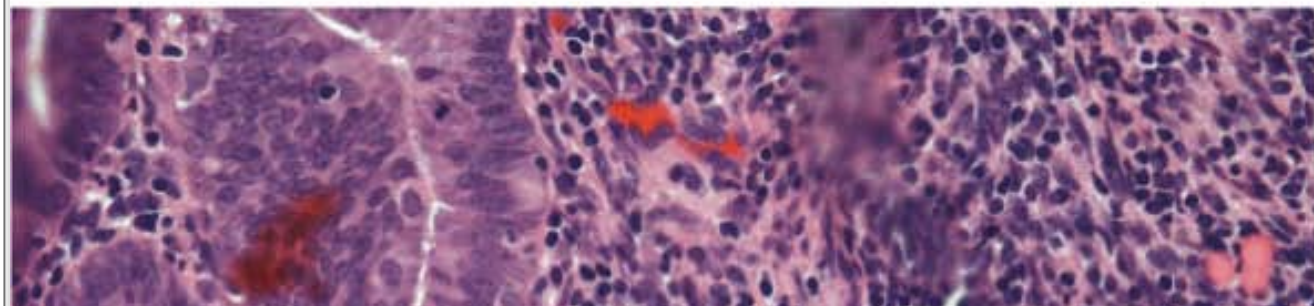
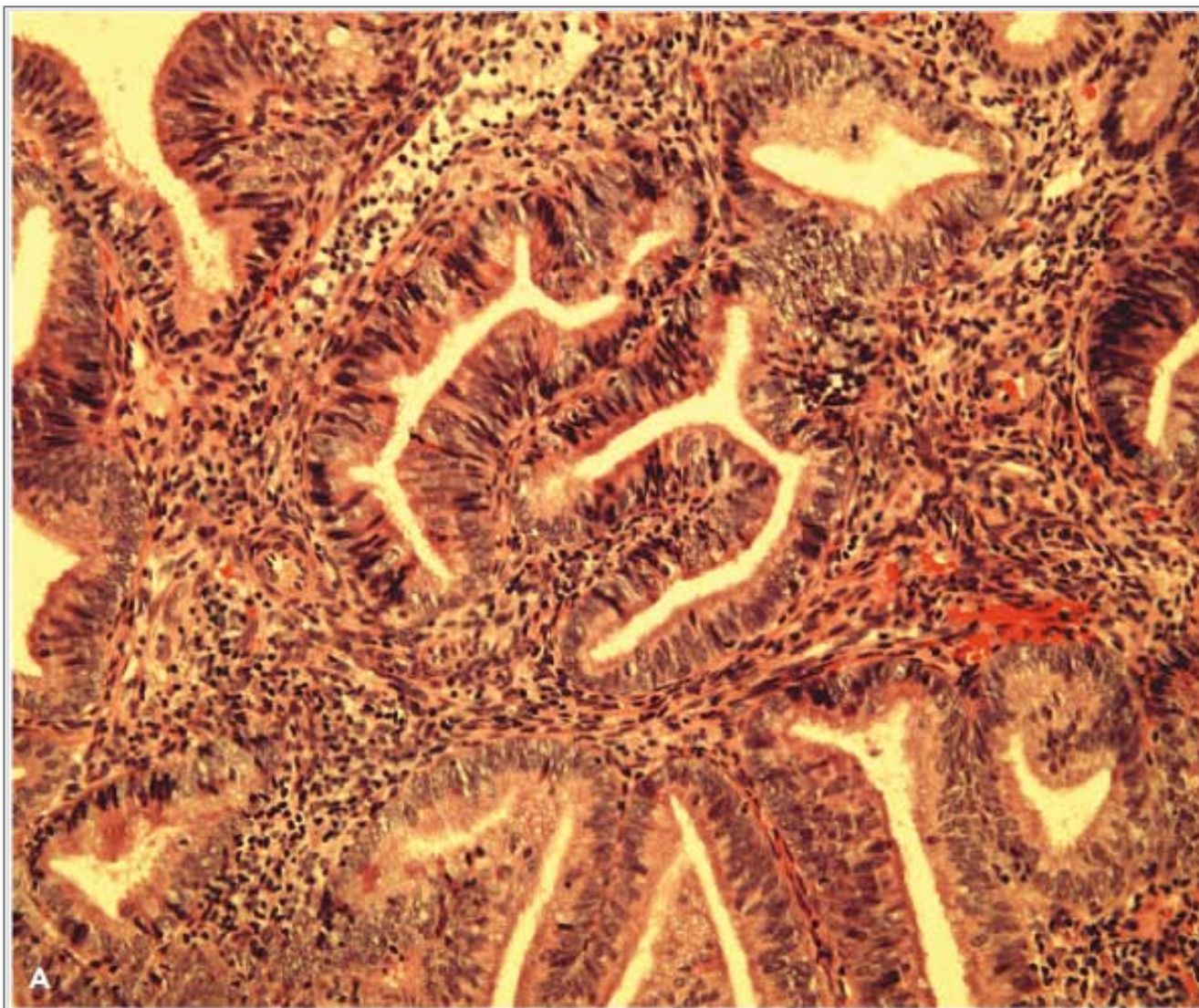
As many as 25% to 43% of patients with atypical hyperplasia detected in an endometrial biopsy or curettage specimen will have an associated, usually well-differentiated, endometrial carcinoma detected during hysterectomy (16). Marked cytologic atypia, a high mitotic rate, and marked cellular stratification are features of atypical endometrial hyperplasia most often associated with the finding of an undiagnosed carcinoma at hysterectomy.

In a report of 85 menopausal women with endometrial hyperplasia treated with medroxyprogesterone acetate (10–20 mg/day), 84% of 65 who did not have cytologic atypia had complete reversal of the lesions, 6% developed recurrent hyperplasia, but none developed cancer at a mean follow-up interval of 7 years (17). By contrast, of 20 patients with cytologic atypia, only 50% responded to progestin, 25% developed recurrent hyperplasia, and 25% developed adenocarcinoma. In another study, hyperplasia resolved in 94% of 32 patients with atypical endometrial hyperplasia who were treated with megestrol acetate (20–40 mg/day); however, relapse occurred in all 7 patients who discontinued progestin therapy (18).

Conversely, **high-dose progestin therapy (medroxyprogesterone acetate, 200 mg/day, or megestrol acetate, 160 mg/day) has been reported to have successfully reversed atypical hyperplasia and well-differentiated endometrial adenocarcinoma in 16 (94%) of 17 and 9 (75%) of 12 premenopausal women younger than age 40, respectively. The average treatment course required to achieve disease regression was 9 month (range**

3–18 months) (19). Subsequent pregnancies after progestin treatment of endometrial hyperplasia and even well-differentiated cancer have occurred and can apparently be enhanced

by the use of assisted reproductive technologies (20).



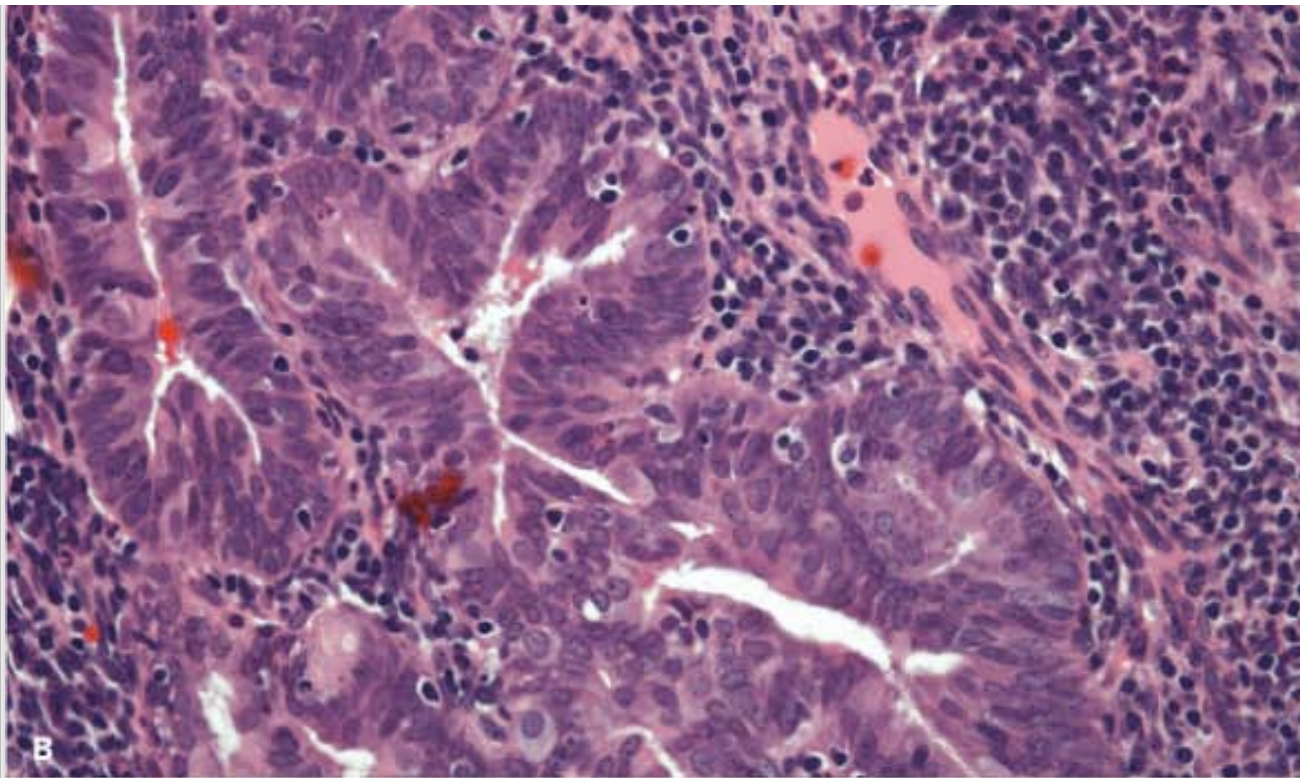


Figure 33.1 Atypical hyperplasia (complex hyperplasia with severe nuclear atypia) of endometrium. A: The proliferative endometrial glands reveal considerable crowding and papillary infoldings. The endometrial stroma, although markedly diminished, can still be recognized between the glands. **B:** Higher magnification demonstrates disorderly nuclear arrangement and nuclear enlargement and irregularity. Some contain small nucleoli. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

Progestin therapy is very effective in reversing endometrial hyperplasia without atypia but is less effective for endometrial hyperplasia with atypia. For women with endometrial hyperplasia without atypia, ovulation induction, cyclical progestin therapy (e.g., *medroxyprogesterone acetate*, 10-20 mg/day for 14 days per month), or continuous progestin therapy (e.g., *megestrol acetate*, 20-40 mg/day) appear to be effective. Continuous progestin therapy with *megestrol acetate* (40-160 mg/day) is probably the most reliable treatment for reversing complex or atypical hyperplasia. Therapy should be continued for 2 to 3 months, and endometrial biopsy should be performed 3 to 4 weeks after completion of therapy to assess response.

Periodic endometrial biopsy or transvaginal ultrasonography is advisable in patients being monitored after progestin therapy for atypical hyperplasia because of the presence of undiagnosed cancer in 25% of cases, the 29% progression rate to cancer, and the high recurrence rate after treatment with progestins. For women with atypical complex hyperplasia who no longer desire fertility, hysterectomy is recommended.

Endometrial Cancer Screening

Screening for endometrial cancer should currently not be undertaken because of the lack of an appropriate, cost-effective, and acceptable test that reduces mortality (21,22,23).

Routine Papanicolaou's (Pap) testing is inadequate and endometrial cytologic assessment is too insensitive and nonspecific to be useful in screening for endometrial cancer even in a high-risk population.

A progesterone challenge test reveals whether the endometrium has been primed by estrogen, but it does not identify abnormal endometrial pathology. Transvaginal ultrasonographic examination of the uterus and endometrial biopsy are too expensive to be employed as screening tests.

Although many risk factors for endometrial cancer have been identified, screening of high-risk individuals could at best detect only one half of all cases of endometrial cancer.

Furthermore, no controlled trials have been carried out to evaluate the effectiveness of screening for endometrial cancer. Screening for endometrial cancer or its precursors may be justified for certain high-risk women, such as those receiving postmenopausal estrogen therapy without progestins and members of families with hereditary nonpolyposis colorectal cancer (24). Conversely, women taking *tamoxifen* receive no benefit from routine screening with transvaginal ultrasonography or endometrial biopsy (25,26).

Fortunately, most patients who have endometrial cancer present with abnormal perimenopausal or postmenopausal uterine bleeding early in the development of the disease, when the tumor is still confined to the uterus. Application of an appropriate and accurate diagnostic test in this situation usually results in early diagnosis, timely treatment, and a high cure rate.

Endometrial Cancer

Clinical Features

Symptoms

Endometrial carcinoma most often occurs in women in the sixth and seventh decades of life, at an average age of 60 years; 75% of cases occur in women older than 50 years of

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age. **About 90% of women with endometrial carcinoma have vaginal bleeding or discharge as their only presenting symptom.** Most women recognize the importance of this symptom and seek medical consultation within 3 months. Some women experience pelvic pressure or discomfort indicative of uterine enlargement or extrauterine disease spread. Bleeding may not have occurred because of cervical stenosis, especially in older patients, and may be associated with hematometra or pyometra, causing a purulent vaginal discharge. This finding is often associated with a poor prognosis (27). **Less than 5% of women diagnosed with endometrial cancer are asymptomatic.** In the absence of symptoms, endometrial cancer is usually detected as the result of investigation of abnormal Pap test results, discovery of cancer in a uterus removed for some other reason, or evaluation of an abnormal finding on a pelvic ultrasonography examination or computed tomography (CT) scan obtained for an unrelated reason. Women who are found to have malignant cells on Pap test are more likely to have a more advanced stage of disease (28).

Abnormal perimenopausal and postmenopausal bleeding should always be taken seriously and be properly investigated, no matter how minimal or nonpersistent. Causes may be nongenital, genital extrauterine, or uterine (29). Nongenital tract sites should be considered based on the history or examination, including testing for blood in the urine and stool.

Invasive tumors of the cervix, vagina, and vulva are usually evident on examination, and any tumors discovered should be biopsied. Traumatic bleeding from an atrophic vagina may account for up to 15% of all causes of postmenopausal vaginal bleeding. This diagnosis can be considered if inspection reveals a thin, friable vaginal wall, but the possibility of a uterine source of bleeding must first be eliminated.

Possible uterine causes of perimenopausal or postmenopausal bleeding include endometrial atrophy, endometrial polyps, estrogen therapy, hyperplasia, and cancer or sarcoma (30,31,32,33) (Table 33.3). Uterine leiomyomas should never be accepted as a cause of postmenopausal bleeding. **Endometrial atrophy is the most common endometrial finding in women with postmenopausal bleeding, accounting for 60% to 80% of such bleeding.** Women with endometrial atrophy have usually been menopausal for about 10

years. **Endometrial biopsy often yields insufficient tissue or only blood and mucus, and usually bleeding ceases after biopsy.** Endometrial polyps account for 2% to 12% of postmenopausal bleeding. Polyps are often difficult to identify with office endometrial biopsy or curettage. Hysteroscopy, transvaginal ultrasonography, or both may be useful adjuncts in identifying endometrial polyps. Unrecognized and untreated polyps may be a source of continued or recurrent bleeding, leading eventually to unnecessary hysterectomy.

Estrogen therapy is an established risk factor for endometrial hyperplasia and cancer. **The risk for endometrial cancer is 4 to 8 times greater in postmenopausal women receiving unopposed estrogen therapy, and the risk increases with time and higher estrogen doses.** This risk can be decreased by the addition of a progestin to the estrogen, either cyclically or continuously. Endometrial biopsy should be performed as indicated to assess

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unscheduled bleeding or annually in women not taking a progestin. **Endometrial hyperplasia occurs in 5% to 10% of patients with postmenopausal uterine bleeding.** The source of excess estrogen should be considered, including obesity, exogenous estrogen, or an estrogen-secreting ovarian tumor. **Only about 10% of patients with postmenopausal bleeding have endometrial cancer.**

<i>Cause of Bleeding</i>	<i>Percentage</i>
Endometrial atrophy	60-80
Estrogen replacement therapy	15-25
Endometrial polyps	2-12
Endometrial hyperplasia	5-10
Endometrial cancer	10

Premenopausal women with endometrial cancer invariably have abnormal

uterine bleeding, which is often characterized as menometrorrhagia or oligomenorrhea, or cyclical bleeding that continues past the usual age of menopause. The diagnosis of endometrial cancer must be considered in premenopausal women if abnormal bleeding is persistent or recurrent or if obesity or chronic anovulation is present.

Signs

Physical examination seldom reveals any evidence of endometrial carcinoma, although **obesity and hypertension are commonly associated constitutional factors**. Special attention should be given to the more common sites of metastasis. Peripheral lymph nodes and breasts should be assessed carefully. Abdominal examination is usually unremarkable, except in advanced cases in which ascites or hepatic or omental metastases may be palpable. On gynecologic examination, the vaginal introitus and suburethral area, as well as the entire vagina and cervix, should be carefully inspected and palpated. Bimanual rectovaginal examination should be performed specifically to evaluate the uterus for size and mobility, the adnexa for masses, the parametria for induration, and the cul-de-sac for nodularity.

Diagnosis

Office endometrial aspiration biopsy is the accepted first step in evaluating a patient with abnormal uterine bleeding or suspected endometrial pathology (34). The diagnostic accuracy of office-based endometrial biopsy is 90% to 98% when compared with subsequent findings at dilation and curettage (D & C) or hysterectomy (35,36,37).

The narrow plastic cannulas are relatively inexpensive, can often be used without a tenaculum, cause less uterine cramping (resulting in increased patient acceptance), and are successful in obtaining adequate tissue samples in more than 95% of cases. If cervical stenosis is encountered, a paracervical block can be performed, and the cervix can be dilated. Premedication with an antiprostaglandin agent can reduce uterine cramping. Complications following endometrial biopsy are exceedingly rare; uterine perforation occurs in only 1 to 2 cases per 1,000. Endocervical curettage may also be performed at the time of endometrial biopsy if cervical pathology is suspected. **A Pap test is an unreliable diagnostic test because only 30% to 50% of patients with endometrial cancer have abnormal Pap test results (38).**

Hysteroscopy and D & C should be reserved for situations in which cervical stenosis or patient tolerance does not permit adequate evaluation by aspiration biopsy, bleeding recurs after a negative endometrial biopsy, or the specimen obtained is inadequate to explain the abnormal bleeding. Hysteroscopy is more accurate in identifying polyps and submucous myomas than endometrial biopsy or D & C alone (39,40,41).

Transvaginal ultrasonography may be a useful adjunct to endometrial biopsy for evaluating abnormal uterine bleeding and selecting patients for additional testing (42,43,44,45). Transvaginal ultrasonography, with or without endometrial fluid instillation (sonohysterography), may be helpful in distinguishing between patients with minimal endometrial tissue whose bleeding is related to perimenopausal anovulation or postmenopausal atrophy and patients with significant amounts of endometrial tissue or polyps who are in need of further evaluation. The finding of an endometrial thickness greater than 4 mm, a polypoid endometrial mass, or a

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collection of fluid within the uterus requires further evaluation. Although most studies agree that an endometrial thickness of 5 mm or less in a postmenopausal woman is consistent with atrophy, more data are needed before ultrasonography findings can be considered to eliminate the need for endometrial biopsy in a patient who has symptoms (46).

Table 33.4 Classification of Endometrial Carcinomas

Endometrioid adenocarcinoma

Variants

Villoglandular or papillary

Secretory

With squamous differentiation

Mucinous carcinoma

Papillary serous carcinoma

Clear cell carcinoma

Squamous carcinoma

Undifferentiated carcinoma

Mixed carcinoma

Pathology

The histologic classification of carcinoma arising in the endometrium is shown in Table 33.4 (12,47).

Endometrioid Adenocarcinoma

The endometrioid type of adenocarcinoma accounts for about 80% of endometrial carcinomas. These tumors are composed of glands that resemble normal endometrial glands; they have columnar cells with basally oriented nuclei, little or no intracytoplasmic mucin, and smooth intraluminal surfaces (see Fig. 33.2). As tumors become less differentiated, they contain more solid areas, less glandular formation, and more cytologic atypia. The well-differentiated lesions may be difficult to separate from atypical hyperplasia.

Criteria that indicate the presence of invasion and are used to diagnose carcinoma are desmoplastic stroma, glands back-to-back without intervening stroma, extensive papillary pattern, and squamous epithelial differentiation. These changes, with the exception of the infiltrating pattern with desmoplastic reaction, require an area of involvement equal to or exceeding one half of a low-power microscopic field (LPF) (>.1 LPF; 4.2 mm in diameter) (48,49).

The differentiation of a carcinoma, expressed as its grade, is determined by architectural growth pattern and nuclear features (Table 33.5). **In the International Federation of Gynecology and Obstetrics (FIGO) grading system proposed in 1989, tumors are grouped into three grades: *grade 1*, 5% or less of the tumor shows a solid growth pattern; *grade 2*, 6% to 50% of the tumor shows a solid growth pattern; and *grade 3*, more than 50% of the tumor shows a solid growth pattern. The presence of notable nuclear atypia that is inappropriate for the architectural grade increases the tumor grade by one.**

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component. This FIGO system is applicable to all endometrioid carcinomas, including its variants, and to mucinous carcinomas. In serous and clear cell carcinomas, nuclear grading takes precedence; however, most investigators believe that these two carcinomas should always be considered high-grade lesions, making grading unnecessary.

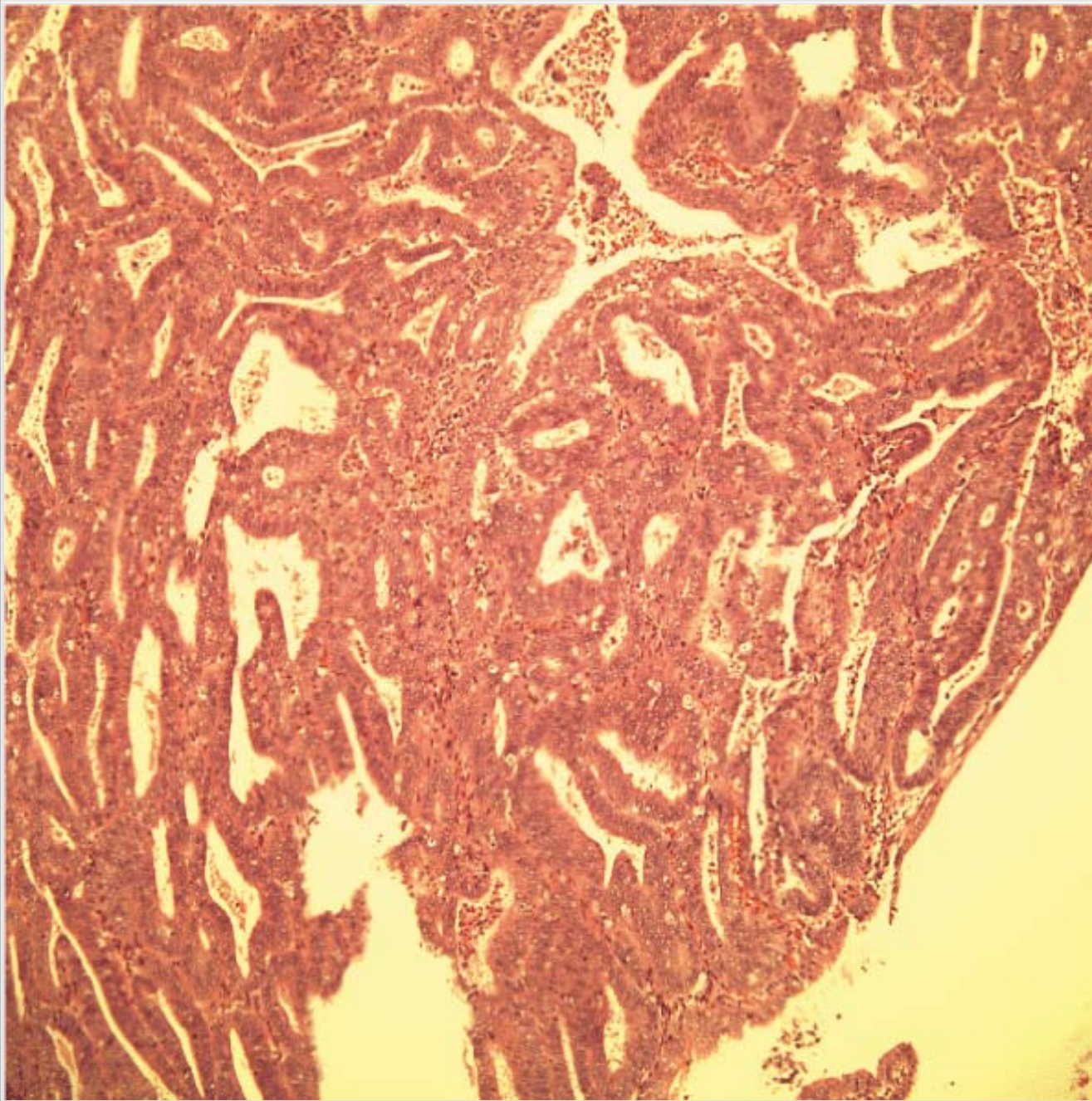


Figure 33.2 Well-differentiated adenocarcinoma of endometrium. The glands and complex papillae are in direct contact with no intervening endometrial stroma, the so-called back-to-back pattern. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

Table 33.5 FIGO Definition for Grading of Endometrial Carcinoma

Histopathologic degree of differentiation:

G1 <5% nonsquamous or nonmorular growth pattern

G2 6%-50% nonsquamous or nonmorular growth pattern

G3 >50% nonsquamous or nonmorular growth pattern

Notes on pathologic grading:

Notable nuclear atypia, inappropriate for the architectural grade, raises a grade 1 (G1) or grade 2 (G2) tumor by one grade.

In serous adenocarcinoma, clear cell adenocarcinoma, and squamous cell carcinoma, nuclear grading takes precedence.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

FIGO, International Federation of Gynecology and Obstetrics.

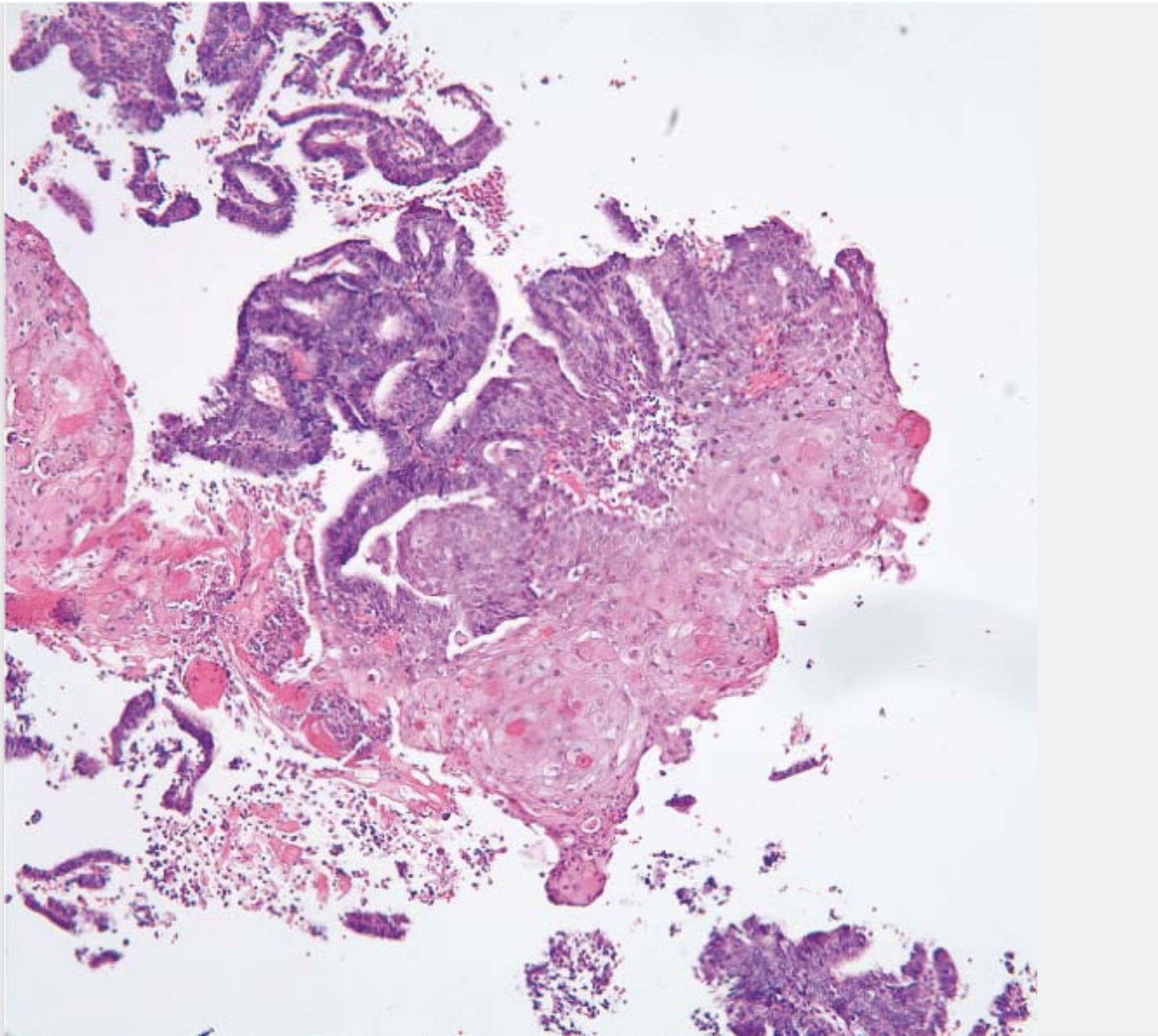


Figure 33.3 Adenocarcinoma with squamous differentiation of endometrium. This lesion is also classified as adenoacanthoma. Squamous cells with eosinophilic cytoplasm and distinct cell borders form solid clusters in the lumina of neoplastic glands. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

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About 15% to 25% of endometrioid carcinomas have areas of squamous differentiation (see Fig. 33.3). In the past, tumors with benign-appearing squamous areas were called *adenoacanthomas*, and tumors with malignant-looking squamous elements were called *adenosquamous carcinomas*. It is now recommended that the term *endometrial carcinoma with squamous differentiation* be used to replace these two designations because the degree of differentiation of the squamous component parallels that of the glandular component and the behavior of the tumor is largely dependent on the grade of the glandular component (50,51).

Avilloglandular configuration is present in about 2% of endometrioid carcinomas (52,53). In these tumors, the cells are arranged along fibrovascular stalks, giving a papillary appearance but maintaining the characteristics of endometrioid cells. The villoglandular variants of endometrioid carcinomas are always well-differentiated lesions that behave like the regular endometrioid carcinomas, and they should be distinguished from papillary serous carcinomas. **Secretory carcinoma is a rare variant of endometrioid carcinoma that accounts for about 1% of cases** (54,55). It occurs mostly in women in their early postmenopausal years. The tumors are composed of well-differentiated glands with intracytoplasmic vacuoles similar to early secretory endometrium. These tumors

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behave as regular well-differentiated endometrioid carcinomas and generally have an excellent prognosis. Secretory carcinoma may be an endometrioid carcinoma that exhibits proggestational changes, but a history of proggestational therapy is rarely elicited. Secretory carcinoma must be differentiated from clear cell carcinoma because both tumors have predominately clear cells. These two tumors can be distinguished by their structure:

secretory carcinomas have uniform glandular architecture, uniform cytology, and low nuclear grade, whereas clear cell carcinomas have more than one architectural pattern and a high nuclear grade.

Mucinous Carcinoma

About 5% of endometrial carcinomas have a predominant mucinous pattern in which more than one half of the tumor is composed of cells with intracytoplasmic mucin (56,57). Most of these tumors have a well-differentiated glandular architecture; their behavior is similar to that of common endometrioid carcinomas, and the prognosis is good. It is important to recognize mucinous carcinoma of the endometrium as an entity and to differentiate it from endocervical adenocarcinoma. Features that favor a primary endometrial carcinoma are the merging of the tumor with areas of normal endometrial tissue, presence of foamy endometrial stromal cells, presence of squamous metaplasia, or presence of areas of typical endometrioid carcinoma. Positive perinuclear immunohistochemical staining with vimentin suggests an endometrial origin (58).

Papillary Serous Carcinoma

About 3% to 4% of endometrial carcinomas resemble serous carcinoma of the ovary and fallopian tube (59,60,61,62). Most often, these tumors are composed of fibrovascular stalks lined by highly atypical cells with tufted stratification (see Fig. 33.4). Psammoma bodies frequently are observed.

***Uterine papillary serous carcinomas (UPSC)* are all considered high-grade lesions.** They are commonly admixed with other histologic patterns, but mixed tumors behave as aggressively as pure serous carcinomas. Serous carcinomas are often associated with lymph-vascular space and deep myometrial invasion. Even when these tumors appear to be confined to the endometrium or endometrial polyps without myometrial or vascular invasion, **they behave more aggressively than endometrioid carcinomas and have a propensity to spread intra-abdominally, simulating the behavior of ovarian carcinoma.** Of patients with clinical stage I disease, more than one half are found to have deep myometrial invasion, three fourths manifest lymph-vascular space invasion (LVSI), and about one half have extrauterine disease detected at surgery.

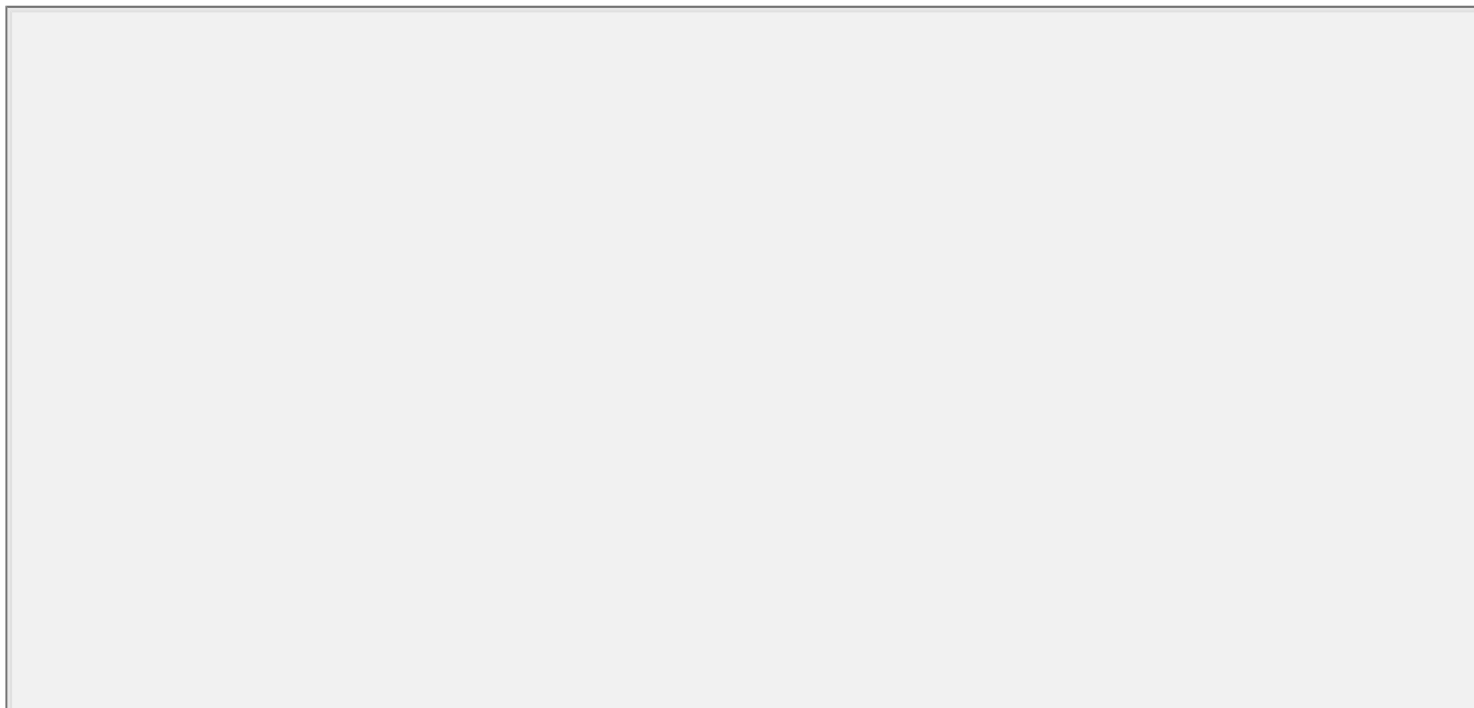
The first description of UPSC, in 1982, noted that this entity usually occurred in

elderly, hypoestrogenic women who presented with advanced-stage disease and accounted for up to one half of deaths from endometrial carcinoma (59). Since then, several reports have documented the aggressive nature and poor prognosis of UPSC. Even when the disease was confined to an endometrioid polyp without other evidence of spread, recurrence developed in more than one half of patients (60,61). More recently, in a report on 50 patients surgically staged with UPSC, extrauterine disease was found in 72%. Presence of lymph node metastases, positive peritoneal cytology, and intraperitoneal tumor did not correlate with increasing myometrial invasion (62).

Clear Cell Carcinoma

Clear cell carcinoma accounts for less than 5% of all endometrial carcinomas (54,63,64). Clear cell carcinoma usually has a mixed histologic pattern, including papillary, tubulocystic, glandular, and solid types.

The cells have highly atypical nuclei and abundant clear or eosinophilic cytoplasm. Often, the cells have a hobnail configuration arranged in papillae with hyalinized stalks (see Fig. 33.5).



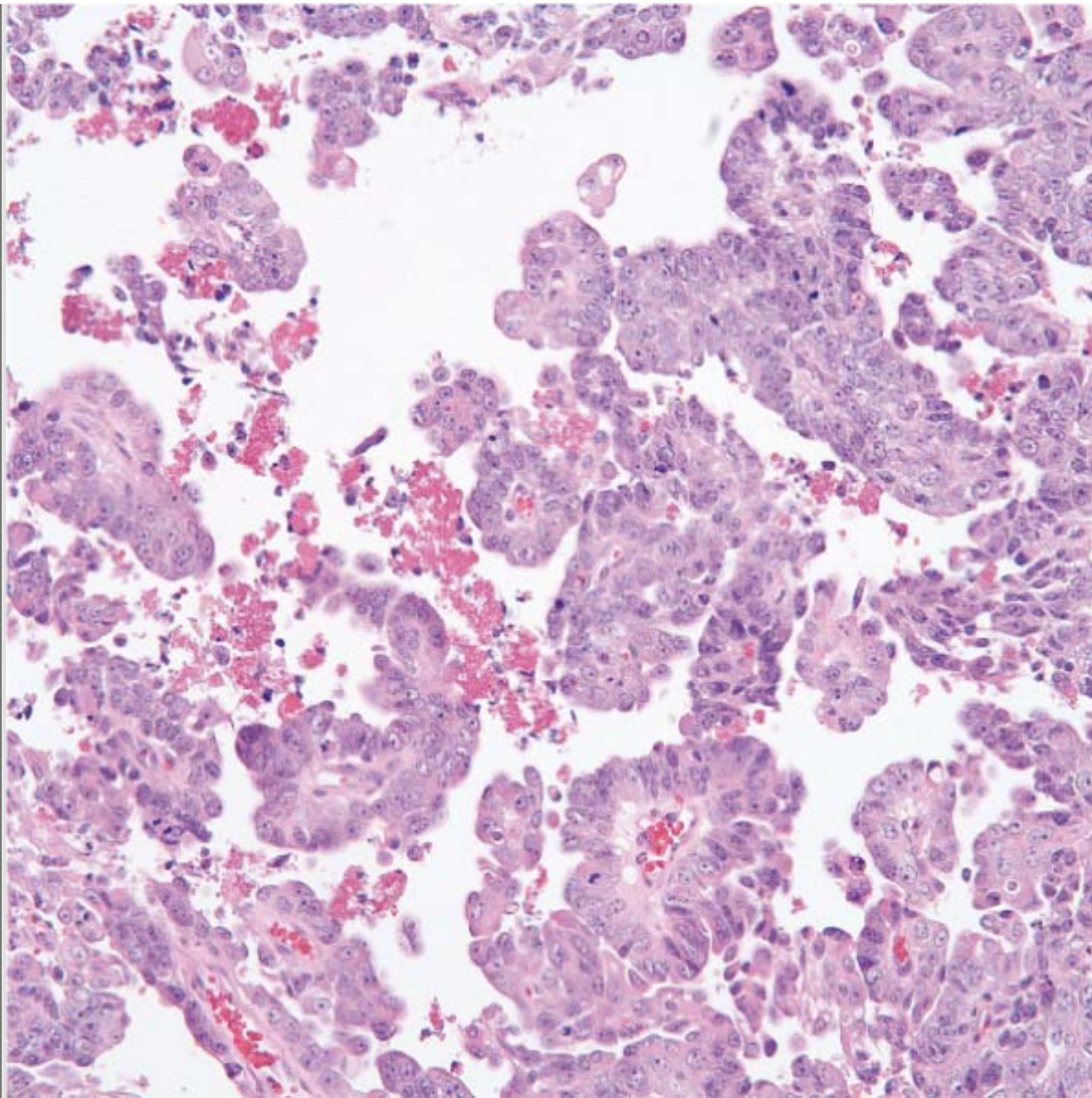


Figure 33.4 Papillary serous carcinoma of endometrium. Branching papillae are supported by delicate fibrovascular cores and lined with columnar cells with moderate nuclear atypism, multiple nucleoli, and mitotic figures. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

Clear cell carcinoma characteristically occurs in older women and is a very aggressive type of endometrial cancer; the prognosis is similar to or worse than that of papillary serous carcinoma. Overall survival rates of 33% to 64% have been reported. Myometrial invasion and LVSI are important prognostic indicators.

Squamous Carcinoma

Squamous carcinoma of the endometrium is rare. Some tumors are pure, but most have a few glands. To establish primary origin within the endometrium, there must be no connection with or spread from cervical squamous epithelium. Squamous carcinoma often is associated with cervical stenosis, chronic inflammation, and pyometra at the time of diagnosis. This tumor has a poor prognosis, with an estimated 36% survival rate in patients with clinical stage I disease (65).

Simultaneous Tumors of the Endometrium and Ovary

Synchronous endometrial and ovarian cancers are the most frequent simultaneously occurring genital malignancies, with a reported incidence of 1.4% to 3.8% (66,67,68,69,70). Most commonly, both the ovarian and endometrial tumor are well-differentiated endometrioid adenocarcinomas of low stage, resulting in an excellent prognosis. Patients often are premenopausal and present with abnormal uterine bleeding. The ovarian

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cancer usually is discovered as an incidental finding and is diagnosed at an earlier stage because of the symptomatic endometrial tumor, leading to a more favorable outcome. Up to 29% of patients with endometrioid ovarian adenocarcinomas have associated endometrial cancer. If more poorly differentiated, nonendometrioid histologic subtypes are present or if the uterine and ovarian tumors are histologically dissimilar, the prognosis is less favorable. Immunohistochemical studies, flow cytometry, and assessment of molecular DNA patterns to detect loss of heterozygosity may be helpful in distinguishing between metastatic

and independent tumors, but the differential diagnosis can usually be determined by conventional clinical and pathologic criteria.

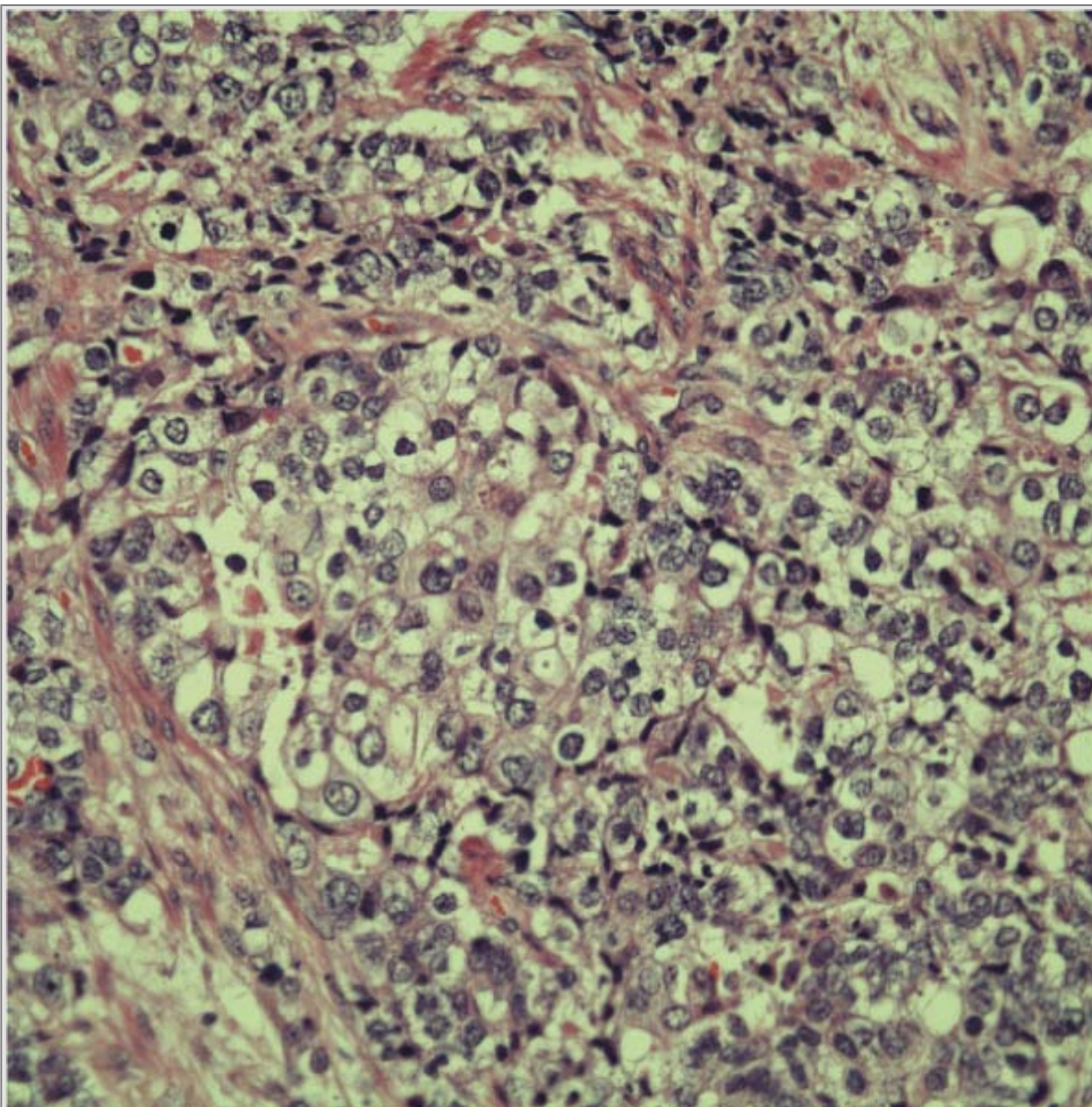


Figure 33.5 Clear cell adenocarcinoma of the endometrium. Back-to-back glands lined by polygonal to columnar cells with distinct cell membrane, abundant granular to clear cytoplasm, and variably sized nuclei (including binucleated and multinucleated forms) with prominent nucleoli (magnification $\times 400$). (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

Pretreatment Evaluation

After establishing the diagnosis of endometrial carcinoma, the next step is to evaluate the patient thoroughly to determine the best and safest approach to management of the disease. A complete history and physical examination is of utmost importance. Patients with endometrial carcinoma are often elderly and obese and have a variety of medical problems, such as diabetes mellitus and hypertension, that affect surgical management. Any abnormal symptoms, such as bladder or intestinal symptoms, should be evaluated.

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On physical examination, attention should be directed to enlarged or suspicious-feeling lymph nodes, abdominal masses, and possible areas of cancer spread within the pelvis. Evidence of distant metastasis or locally advanced disease in the pelvis, such as gross cervical involvement or parametrial spread, may alter the treatment approach. Stool should be tested for occult blood.

Chest radiography should be performed to exclude pulmonary metastasis and to evaluate the cardiorespiratory status of the patient. Other routine preoperative studies should include electrocardiography, complete blood and platelet counts, serum chemistries (including renal and liver function tests), blood type and screen, and urinalysis. Other preoperative or staging studies are neither required nor necessary for most patients with endometrial cancer. **Studies such as cystoscopy, colonoscopy, intravenous pyelography, barium enema, and CT scanning of the abdomen and pelvis are not indicated unless dictated by patient symptoms, physical findings, or other laboratory tests** (71). Ultrasonography and magnetic resonance imaging (MRI) can be used to assess myometrial invasion preoperatively with a fairly high degree of accuracy (72). This information may be of use in planning the surgical procedure with regard to whether lymph node sampling should be undertaken.

Serum CA125, an antigenic determinant that is elevated in 80% of patients with advanced epithelial ovarian cancers, also is elevated in most patients with advanced or metastatic endometrial cancer (73). In one study, 23 of 81 patients with apparently localized disease preoperatively had elevated CA125 levels. At surgery, 20 (87%) of these 23 patients with an elevated CA125 were found to have extrauterine disease, whereas only 1 of 58 patients with a normal CA125 had disease spread outside the uterus (74). Another study found that 78% of endometrial cancer patients with lymph node metastases had an elevated preoperative CA125 level (75). Preoperative measurement of serum CA125 may, therefore, help determine the extent of surgical staging and, if elevated, may be useful as a tumor marker in assessing response to subsequent therapy (76,77).

Clinical Staging

Clinical staging, according to the 1971 FIGO system (Table 33.6), **should be performed in patients who are deemed not to be surgical candidates because of their poor medical condition or the spread of their disease** (78). With improvements in preoperative and postoperative care, anesthesia administration, and surgical techniques, almost all patients are medically suitable for operative therapy. One study reported an

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operability rate of 87% in a series of 595 consecutive patients with clinical early-stage endometrial cancer (79). A small percentage of patients will not be candidates for surgical staging because of gross cervical involvement, parametrial spread, invasion of the bladder or rectum, or distant metastasis.

Table 33.6 FIGO Clinical Staging of Endometrial Carcinoma (1971)

Stage	Characteristic
I	Confined to the corpus
Ia G123	Uterine cavity <8 cm
Ib G123	Uterine cavity >8 cm
II	Involves the corpus and cervix, but has not extended outside the uterus
III	Extends outside the uterus, but not outside the true pelvis
IV	Extends outside the true pelvis or obviously involves the mucosa of the bladder or rectum
IVa	Spread to adjacent organs
IVb	Spread to distant organs

FIGO, International Federation of Gynecology and Obstetrics.

Table 33.7 FIGO Surgical Staging for Endometrial Carcinoma (1988)	
Stage	Finding
Ia G123	No myometrial invasion
Ib G123	< ½ Myometrial invasion
Ic G123	> ½ Myometrial invasion
IIa G123	Extension to endocervical glands
IIb G123	Cervical stromal invasion
IIIa G123	Positive uterine serosa, adnexa, and/or peritoneal cytology
IIIb G123	Vaginal metastasis
IIIc G123	Metastasis to pelvic and/or para-aortic lymph nodes
IVa G123	Tumor invasion of bladder and/or bowel mucosa
IVb	Distant metastasis including intra-abdominal and/or inguinal lymph nodes

FIGO, International Federation of Gynecology and Obstetrics.

Surgical Staging

Most patients with endometrial cancer should undergo surgical staging based on the 1988 FIGO system (80,81,82) (Table 33.7). At a minimum, the surgical procedure

should include sampling of peritoneal fluid for cytologic evaluation, exploration of the abdomen and pelvis with biopsy or excision of any extrauterine lesions suggestive of metastatic cancer, extrafascial hysterectomy, and bilateral salpingo-oophorectomy. The uterine specimen should be opened and tumor size (83), depth of myometrial involvement (84,85,86), and cervical extension assessed. Any suspicious pelvic and para-aortic lymph nodes should be removed for pathologic examination.

Additionally, clinically negative retroperitoneal lymph nodes should be sampled in all patients with one or more of the risk factors noted in Table 33.8. Tumor histology and depth of myometrial invasion appear to be the two most important factors in determining the risk for lymph node metastasis (81,82). The overall incidence of lymph node metastasis in clinical stage I endometrial cancer is about 3% in grade 1, 9% in grade 2, and 18% in grade 3 tumors (Table 33.9). Less than 5% of patients with no myometrial invasion or with superficial (<50%) myometrial invasion have lymph node metastasis, compared with about 20% of patients with deep (>50%) myometrial invasion (Table 33.10). **Pelvic**

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lymph node metastases are present in less than 5% of grade 1 and 2 tumors with superficial myometrial invasion, in about 15% of grade 1 and 2 tumors with deep myometrial invasion or grade 3 tumors with superficial invasion, and in more than 40% of grade 3 tumors with deep myometrial invasion (see Fig. 33.6). About one half to two thirds of patients with positive pelvic lymph nodes also have para-aortic lymph node metastases, but the aortic nodes are seldom involved in the absence of pelvic nodal disease. Cervical involvement is associated with about a 15% risk of pelvic or para-aortic node metastasis (82). **The incidence of lymph node metastasis also correlates with tumor size (<2 cm, 4%; >2 cm, 15%; entire cavity, 35%)** (83). Extrauterine spread of disease increases the risk of pelvic and para-aortic nodal metastasis. Adnexal metastasis increases the risk for pelvic and para-aortic nodal metastasis to 32% and 20%, respectively. Of patients with positive peritoneal cytology, 25% have positive pelvic nodes, and 19% have positive para-aortic nodes (82).

Table 33.8 Indications for Selective Pelvic and Para-aortic Lymph Node Dissection in Endometrial Cancer

 Tumor histology clear cell, serous, squamous, or grade 2-3 endometrioid

 Myometrial invasion $> \frac{1}{2}$

 Isthmus-cervix extension

 Tumor size > 2 cm

 Extrauterine disease

Table 33.9 Relationship of Grade to Lymph Node Metastasis in Clinical Stage I Endometrial Carcinoma

Grade	No.	Pelvic Nodes		Aortic Nodes	
		No.	%	No.	%
1	180	5	3	3	2
2	288	25	9	14	5
3	153	28	18	17	11

From **Creasman WT, Morrow CP, Bundy BN, et al.** Surgical pathologic spread patterns of endometrial cancer. *Cancer* 1987;60:2035-2041, with permission.

Selective pelvic and high common iliac/para-aortic lymph node dissections should, therefore, be performed in the presence of adnexal or cervical involvement, a large (> 2 cm) tumor, deep ($> 50\%$) myometrial invasion, or a moderate to poorly differentiated endometrioid, papillary serous, or clear cell tumor. Because fewer than 10% of patients with lymphatic metastasis have grossly enlarged nodes, palpation is not an acceptable alternative to biopsy. Conversely, because almost

all patients with lymph node metastases have one or more of the aforementioned risk factors, lymph node biopsies are not required in patients assessed intraoperatively to be at very low risk for lymphatic metastasis (ie, patients with small [<2 cm] grade 1 endometrial cancers with only superficial myometrial invasion). In addition, partial omentectomy should be considered in some high-risk patients, especially those with papillary serous and mixed mullerian tumors, which have a propensity for intra-abdominal spread and upper-abdominal recurrence.

Table 33.10 Relationship of Myometrial Invasion to Lymph Node Metastasis in Clinical Stage I Endometrial Carcinoma

<i>Myometrial Invasion</i>	<i>No.</i>	<i>Pelvic Nodes</i>		<i>Aortic Nodes</i>	
		<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
None	87	1	1	1	1
Inner third	279	15	5	8	3
Middle third	116	7	6	1	1
Outer third	139	35	25	24	17

From **Creasman WT, Morrow CP, Bundy BN, et al.** Surgical pathologic spread patterns of endometrial cancer. *Cancer* 1987; 60: 2035-2041, with permission.

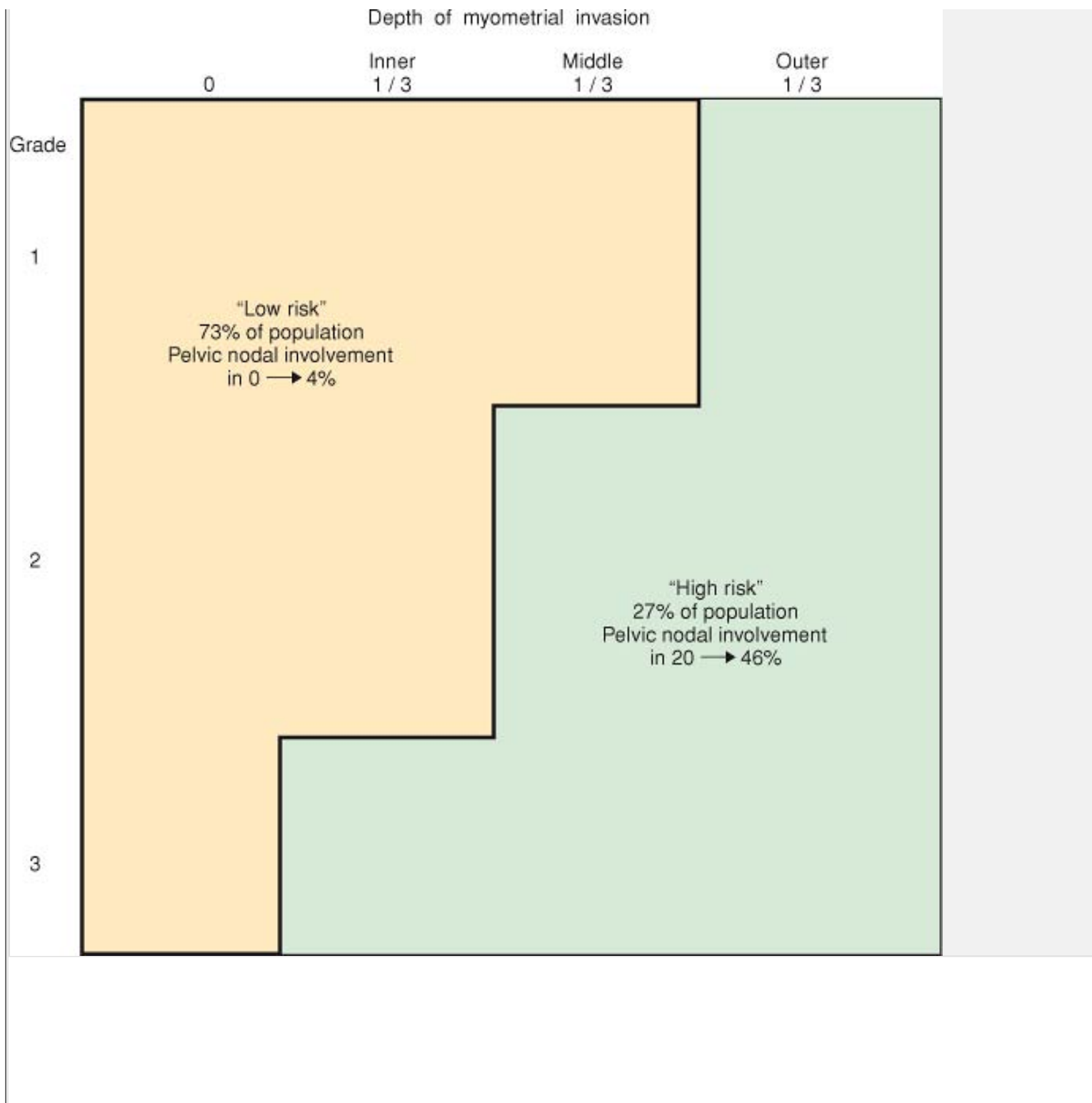


Figure 33.6 The risk for pelvic lymph node metastasis with grade and depth of myometrial penetration in clinical stage I endometrial cancer. Adjuvant pelvic irradiation is recommended for the high-risk group but not for the low-risk group. (From **DiSaia PJ, Creasman WT.** Management of endometrial adenocarcinoma, stage I with surgical staging followed by tailored adjuvant radiation therapy. *Clin Obstet Gynecol* 1986;13:751, with permission.)

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Extended surgical staging, including selective pelvic and para-aortic lymphadenectomy, in patients with endometrial cancer does not significantly add to the morbidity from hysterectomy, which is primarily related to other factors, such as patient weight, age, and race; operating time; and surgical technique. The complication rate with this type of surgery is about 20%; about 6% of these complications are serious. The most common complications are wound infection, embolic phenomena, excess blood loss, gastrointestinal injury or obstruction, and lymphocyst formation (87,88,89,90,91).

In addition, **selective pelvic and para-aortic lymphadenectomy may have a therapeutic effect** (92,93). One study noted that patients who underwent pelvic lymph node sampling had a significant survival advantage overall in both low-risk and high-risk groups (92). Likewise, para-aortic lymphadenectomy has been found to be a significant positive predictor for recurrence-free survival in patients with high-risk endometrial cancer. Among 137 high-risk patients, the 5-year progression-free survival rate was 77% for patients undergoing para-aortic lymph node dissection, compared with 62% for patients not having para-aortic lymphadenectomy (93).

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Table 33.11. Surgical-Pathologic Findings in Clinical Stage I Endometrial Cancer

<i>Surgical-Pathologic Finding</i>	<i>Percentage of Patients</i>
Histology	
Adenocarcinoma	80
Adenosquamous	16
Other (papillary serous, clear cell)	4
Grade	
1	29
2	46
3	25
Myometrial invasion	
None	14
Inner third	45
Middle third	19
Outer third	22
Lymph-vascular space invasion	15
Isthmic tumor	16
Adnexal involvement	5
Positive peritoneal cytology	12
Pelvic lymph node metastasis	9
Aortic lymph node metastasis	6
Other extrauterine metastasis	6
Modified from Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. <i>Cancer</i> 1987;60:2035-2041, with permission.	

Surgical staging is extremely important when one considers the poor correlation of preoperative evaluation and clinical staging with surgical and pathologic findings. In a comparison of preoperative findings with surgical pathology, tumor histology was changed in 27% of patients, tumor grade was changed in 34% of patients, and stage was changed in 51% of patients (94). In the Gynecologic Oncology Group (GOG) series, 22% of 621 patients with clinical stage I endometrial cancer had evidence, discovered at staging laparotomy, of extrauterine spread, including lymph node metastasis, adnexal spread, peritoneal implants, and positive peritoneal cytology (82) (Table 33.11). In two other studies, extrauterine spread was found in clinical stages I (19%) and II (40%), with an overall incidence of 23.4% (95) and in

19 (12.3%) of 154 clinical stage I and II patients (96). In a retrospective comparison of clinical and surgical stage with respect to survival in 156 patients with endometrial cancer, surgery resulted in an increase in the stage in 12.4% and 27.3% of clinical stage I and II patients, respectively (97). Surgical stage was found to be the most important factor affecting prognosis.

All patients with endometrial cancer who are taken to the operating room for primary therapy should, therefore, be prepared to undergo surgical staging. Such staging may include selective pelvic and para-aortic lymph node dissection, in addition to hysterectomy and salpingo-oophorectomy, based on the intraoperative assessment of risk for lymph node metastasis or other extrauterine spread.

Surgical staging identifies most patients with extrauterine disease and has a significant impact on treatment decisions. Surgical staging also identifies patients with uterine risk factors, including deep myometrial invasion, cervical extension, and LVSI. The identification of these factors allows for a more informed approach to the use of postoperative adjuvant radiotherapy, and it is hoped that this approach will improve survival and spare many patients unnecessary exposure to radiation (98,99,100,101,102,103,104,105).

Table 33.12 Prognostic Variables in Endometrial Carcinoma

Age
Histologic type
Histologic grade
Myometrial invasion
Lymph-vascular space invasion
Isthmus-cervix extension
Adnexal involvement
Lymph node metastasis
Intraperitoneal tumor
Tumor size
Peritoneal cytology
Hormone receptor status
DNA ploidy/proliferative index
Genetic/molecular tumor markers

Prognostic Variables

Although stage of disease is the most significant variable affecting survival, a number of other individual prognostic factors for disease recurrence or survival have been identified, including tumor grade, histopathology, depth of myometrial invasion, patient age, and surgical—pathologic evidence of extrauterine disease spread (Table 33.12). Other factors, such as tumor size, peritoneal cytology, hormone receptor status, flow cytometric analysis, and oncogene perturbations, have also been implicated as having prognostic importance.

Age

In general, younger women with endometrial cancer have a better prognosis than older women. Two reports observed no deaths related to disease in patients with endometrial cancer diagnosed before 50 years of age (98,106). Another series demonstrated a 60.9% 5-year survival rate for patients older than 70 years of age, compared with 92.1% survival rate for patients younger than 50 years of age (107). Decreased survival was associated with an increased risk for extrauterine spread (38% versus 21%) and deep myometrial invasion (57% versus 24%) for these two groups. The GOG reported 5-year survival rates of 96.3% for patients 50 years of age or younger, 87.3% for patients 51 to 60 years, 78% for patients 61 to 70 years, 70.7% for patients 71 to 80 years, and 53.6% for patients older than 80 years (108).

Increased risk for recurrence in older patients has also been related to a higher incidence of grade 3 tumors or unfavorable histologic subtypes; however, age appears to be an independent prognostic variable. Increasing patient age has been found to be independently associated with disease recurrence in endometrial cancer. In one study, the mean age at diagnosis of patients who had recurrence or died of disease was 68.6 years, compared with 60.3 years for patients without recurrence. For every 1-year increase in age, the estimated rate of recurrence increased 7%. None of the patients younger than 50 years of age developed recurrent cancer, compared with 12% of patients aged 50 to 75 years and 33% of patients older than 75 years (103).

Histologic Type

Nonendometrioid histologic subtypes account for about 10% of endometrial cancers and carry an increased risk for recurrence and distant spread (109,110). In a retro

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spective review of 388 patients treated at the Mayo Clinic for endometrial cancer, 52 (13%) had an uncommon histologic subtype, including 20 adenosquamous, 14 papillary serous, 11 clear cell, and 7 undifferentiated carcinomas. In contrast to the 92% survival rate among patients with endometrioid tumors, the overall survival for patients with one of these more aggressive subtypes was only 33%. At the time of surgical staging, 62% of the patients with an unfavorable histologic subtype had extrauterine spread of disease (109).

Histologic Grade

Histologic grade of the endometrial tumor is strongly associated with prognosis (82,88,100,101,102,103,104,105). In one study, recurrences developed in 7.7% of grade 1 tumors, 10.5% of grade 2 tumors, and 36.1% of grade 3 tumors. Patients with grade 3 tumors were more than 5 times more likely to have a recurrence than were patients with grade 1 and 2 tumors. The 5-year disease-free survival rates for patients with grades 1 and 2 tumors were 92% and 86%, respectively, compared with 64% for patients with grade 3 tumors (103). Another study reported similar results, noting recurrences in 9% of patients with grade 1 and 2 tumors compared with 39% of patients with grade 3 lesions (101). Increasing tumor anaplasia is associated with deep myometrial invasion, cervical extension, lymph node metastasis, and both local recurrence and distant metastasis.

Myometrial Invasion

Because access to the lymphatic system increases as cancer invades into the outer one half of the myometrium, increasing depth of invasion has been associated with increasing likelihood of extrauterine spread and recurrence (81,102,105).

The association of depth of myometrial invasion with extrauterine disease and lymph node metastases has been confirmed (81). Of patients without demonstrable myometrial invasion, only 1% had pelvic lymph node metastasis, compared with patients with outer one third myometrial invasion who had 25% pelvic and 17% aortic lymph node metastases. Survival also decreases with increasing depth of myometrial invasion. In general, patients with noninvasive or superficially invasive tumors have an 80% to 90% 5-year survival rate, whereas those with deeply invasive tumors have a 60% survival rate. The most sensitive indicator

of the effect of myometrial invasion on survival is distance from the tumor—myometrial junction to the uterine serosa. Patients with tumors that are less than 5 mm from the serosal surface are at much higher risk for recurrence and death than those with tumors greater than 5 mm from the serosal surface (111,112).

Lymph—Vascular Space Invasion

Lymph-vascular space invasion appears to be an independent risk factor for recurrence and death from all types of endometrial cancer (94,112,113,114). The overall incidence of LVSI in early endometrial cancer is about 15%, although it increases with increasing tumor grade and depth of myometrial invasion. One study reported LVSI in 2% of grade 1 tumors and 5% of superficially invasive tumors, compared with 42% of grade 3 tumors and 70% of deeply invasive tumors (113). Another study reported deaths in 26.7% of patients with clinical stage I disease who had LVSI, compared with 9.1% of those without LVSI (93). Likewise, an 83% 5-year survival rate has been reported for patients without demonstrable LVSI, compared with a 64.5% survival rate for those in whom LVSI was present (114). Using multivariate analysis, only depth of myometrial invasion, DNA ploidy, and vascular invasion—associated changes correlated significantly with survival of patients with stage I endometrial adenocarcinomas in another report (115).

Isthmus and Cervix Extension

The location of the tumor within the uterus is important. Involvement of the uterine isthmus, cervix, or both is associated with an increased risk for extrauterine disease and lymph node metastasis as well as recurrence. One study reported that if the fundus of the uterus alone was involved with tumor, there was a 13% recurrence rate, whereas if the lower uterine segment or cervix was involved with occult tumor, there was a 44%

recurrence rate (100). A subsequent GOG study found that tumor involvement of the isthmus or cervix without evidence of extrauterine disease was associated with a 16% recurrence rate and a relative risk of 1.6 (88). Patients with cervical involvement also tended to have higher-grade, larger, and more deeply invasive tumors, undoubtedly contributing to the increased risk for recurrence.

Adnexal Involvement

Most patients with adnexal spread have other poor prognostic factors that place them at high risk for recurrence. For the 20% of patients with adnexal spread as their only high-risk factor, however, the survival rate has been reported to be as high as 85% (88).

Peritoneal Cytology

The significance of malignant peritoneal cytology in endometrial cancer is a controversial issue (116). Several reports in the literature have noted increased recurrence rates and decreased survival rates and, on this basis, have recommended treatment for positive cytology (117,118,119). In an early report, positive peritoneal cytology was noted in 26 (16%) of 167 patients with clinical stage I adenocarcinoma of the endometrium (117). Recurrent cancer developed in 10 (38%) of these 26 patients, compared with 14 (10%) of 141 patients with negative cytology. Positive peritoneal cytology was found to be associated with deep myometrial invasion, cervical involvement, adnexal spread, and lymph node metastasis, as well as a propensity for intra-abdominal disease recurrence. Several subsequent reports supported the observation that positive peritoneal cytology was associated with an increased risk for cancer recurrence (118,119). Most of the studies included patients with other evidence of extrauterine disease spread and were performed without appropriate multivariate analysis and with patients who were incompletely staged. The GOG study, however, critically analyzed 1,180 clinical stage I and II endometrial cancer patients in whom appropriate surgical and pathologic staging was performed (88). Considering only the 697 patients for whom peritoneal cytology status and adequate follow-up were available, 25 (29%) of 86 patients with positive cytology developed recurrence, compared with 64 (10.5%) of 611 patients with negative cytology. They noted, however, that 17 of the 25 recurrences in the positive cytology group were outside the peritoneal cavity.

In contrast to these reports, **an equal number of studies have found no significant relationship between malignant peritoneal cytology and an increased incidence of disease recurrence in early endometrial cancer** (119,120,121,122). In a prospective evaluation of peritoneal cytology in 157 patients with clinical stage I endometrial cancer who underwent primary surgical therapy (120), no treatment was directed specifically to positive cytology. Positive cytology was not significantly associated with disease recurrence. Recurrence developed in 5 (17%) of 30 patients with positive cytology and in 11 (9%) of 127 patients with negative cytology. Of the 5 patients with positive

peritoneal cytology who had disease recurrence, only one recurrence arose within the peritoneal cavity. Patients with malignant washings often had other poor prognostic factors: 37%, deep myometrial invasion; 37%, grade 3 tumors; 17%, positive lymph nodes. Disease recurred in none of the patients with positive cytology who had no other poor prognostic factors. A subsequent study confirmed by multivariate analysis that positive peritoneal cytology was not an independent prognostic factor for endometrial cancer recurrence. Only 6 (22%) of the 27 patients with positive cytology as their only evidence of extrauterine disease spread suffered a recurrence despite no therapy directed toward this finding (103). **Positive peritoneal cytology seems to have an adverse effect on survival only if the endometrial cancer has spread to the adnexa, peritoneum, or lymph nodes, not if the disease is otherwise confined to the uterus** (121,122,123). More grade 3 tumors (41% versus 19%), vascular invasion (18% versus 6%), adnexal spread (18% versus 4%), lymph node metastasis (29% versus 8%), and intraperitoneal spread (18% versus 2%) occurred in patients with positive peritoneal cytology, which contributed to the overall recurrence rate of 47% in these patients (121). The 5-year survival rate for patients with positive peritoneal cytology with disease otherwise confined to the uterus exceeds 90%.

The following conclusions may be reached regarding the prognostic implications of positive peritoneal cytology:

- **Positive peritoneal cytology is associated with other known poor prognostic factors.**
- **Positive peritoneal cytology in the absence of other evidence of extrauterine disease or poor prognostic factors probably has no significant effect on recurrence and survival.**
- **Positive peritoneal cytology, when associated with other poor prognostic factors or extrauterine disease, increases the likelihood for distant as well as intra-abdominal disease recurrence and has a significant adverse effect on survival.**
- **Use of several different therapeutic modalities has not resulted in any proven benefit to patients with endometrial cancer and positive peritoneal cytology.**

Lymph Node Metastasis

Lymph node metastasis is the most important prognostic factor in clinical early-stage endometrial cancer. Of patients with clinical stage I disease, about 10% will have pelvic and 6% will have para-aortic lymph node metastases. Patients with lymph node metastases have almost a sixfold higher likelihood of developing recurrent cancer than patients without lymph node metastases. One study reported a recurrence rate of 48% with positive lymph nodes, including 45% with positive pelvic nodes and 64% with positive aortic nodes, compared with 8% with negative nodes. **The 5-year disease-free survival rate for patients with lymph node metastases was 54%, compared with 90% for patients without lymph node metastases** (103). The GOG found that the presence or absence of para-aortic lymph node metastases was of paramount importance in determining prognosis. Of 48 para-aortic node—positive patients, 28 (58%) developed progressive or recurrent cancer, and only 36% of these patients were alive at 5 years, compared with 85% of patients without para-aortic node involvement (87).

Intraperitoneal Tumor

Extrauterine metastasis, excluding peritoneal cytology and lymph node metastasis, occurs in about 4% to 6% of patients with clinical stage I endometrial cancer.

Gross intraperitoneal spread has been highly correlated with lymph node metastases; one study noted that 51% of patients with intraperitoneal tumor had positive lymph nodes, whereas only 7% of patients without gross peritoneal spread had positive nodes (82). Extrauterine spread other than lymph node metastasis is also significantly associated with tumor recurrence. Another study found that 50% of patients with extrauterine disease developed recurrence, compared with 11% of patients without extrauterine disease, making recurrence almost 5 times more likely in patients with extrauterine disease spread. **The 5-year disease-free survival rate for patients with nonlymphatic extrauterine disease was 50%, compared with 88% in other patients** (103).

Tumor Size

Tumor size is a significant prognostic factor for lymph node metastasis and survival in patients with endometrial cancer (83,124). One report determined tumor size in 142

patients with clinical stage I endometrial cancer and found lymph node metastasis in 4% of patients with tumors 2 cm or smaller, in 15% of patients with tumors larger than 2 cm, and in 35% of patients with tumors involving the entire uterine cavity (83). Tumor size better defined an intermediate-risk group for lymph nodes metastasis (ie, patients with grade 2 tumors with less than 50% myometrial invasion). Overall, these patients had a 10% risk for lymph node metastasis, but there was no nodal metastasis associated with tumors 2 cm or

smaller, compared with 18% when tumors were larger than 2 cm. Five-year survival rates were 98% for patients with tumors 2 cm or smaller, 84% for patients with tumors larger than 2 cm, and 64% for patients with tumors involving the whole uterine cavity (124).

Hormone Receptor Status

Estrogen receptor and progesterone receptor levels have been shown to be prognostic indicators for endometrial cancer independent of grade in several studies (125,126,127,128,129,130,131). Patients whose tumors are positive for one or both receptors have longer survival times than patients whose carcinomas lack the corresponding receptors. Even patients with metastasis have an improved prognosis with receptor-positive tumors (128). Progesterone receptor levels appear to be stronger predictors of survival than estrogen receptor levels, and the higher the absolute level of the receptors, the better the prognosis.

DNA Ploidy and Proliferative Index

About two thirds of endometrial adenocarcinomas have a diploid DNA content as determined by flow cytometric analysis (115,129,132,133,134,135,136,137,138,139,140). **The proportion of nondiploid tumors increases with stage, lack of tumor differentiation, and depth of myometrial invasion.** In several studies, DNA content has been related to clinical course of the disease, with death rates generally reported to be higher in women whose tumors contained aneuploid populations of cells. The proliferative index also is related to prognosis.

Genetic and Molecular Markers

Mutations in codons 12 or 13 of the **K-ras** oncogene have been reported in 10% to 20% of endometrial adenocarcinomas (141). **The presence of mutations of K-ras appears to be**

an independent unfavorable prognostic factor (142,143). E-cadherin, an oncogene responsible for cell-to-cell adhesion that seems to play a critical role in initiation and progression of endometrial neoplasia, is found in 5% to 50% of endometrial carcinomas. Reduced expression of e-cadherin is related to advanced stage disease (144,145). Overexpression of the HER-2/*neu* oncogene, which encodes for a cell surface glycoprotein that is similar to the human epidermal growth factor receptor, has been identified in 10% to 15% of endometrial adenocarcinomas. It is more frequently found in women with metastatic disease, and overexpression has been related to diminished progression-free survival (146,147,148). **Alteration of the tumor suppressor gene *p53* has been demonstrated in about 20% of endometrial carcinomas and has been associated with papillary serous cell type, advanced stage, and poor prognosis** (139,149,150,151). Expression of *MIB-1* (*Ki-*), a proliferation marker, has been associated with extrauterine disease spread and decreased survival (152). Analysis of homozygous deletions on chromosome 10q23 in human cancer has led to the discovery of the *PTEN* tumor-suppressor gene. Mutations and deletions of the *PTEN* gene occur in 30% to 80% of endometrial cancers, which tend to be endometrioid, well differentiated, and minimally invasive (153,154,155). **Microsatellite instability, present in about 20% of endometrial cancers, appears to be restricted to endometrioid adenocarcinomas and is associated with other molecular features that predict a favorable outcome, including *PTEN* mutation and absence of *p53* overexpression** (156,157).

Treatment

An algorithm for the management of patients with clinical stage I and II endometrial cancer is presented in Figure 33.7.

Surgery

Abdominal Hysterectomy

Total abdominal hysterectomy and bilateral salpingo-oophorectomy are the primary operative procedures for carcinoma of endometrium. The adnexa should be removed because they may be the site of microscopic metastasis, and patients with

endometrial carcinoma are at increased risk for ovarian cancer occurring either simultaneously or developing later. Removal of a segment of vagina below the cervix is not necessary.

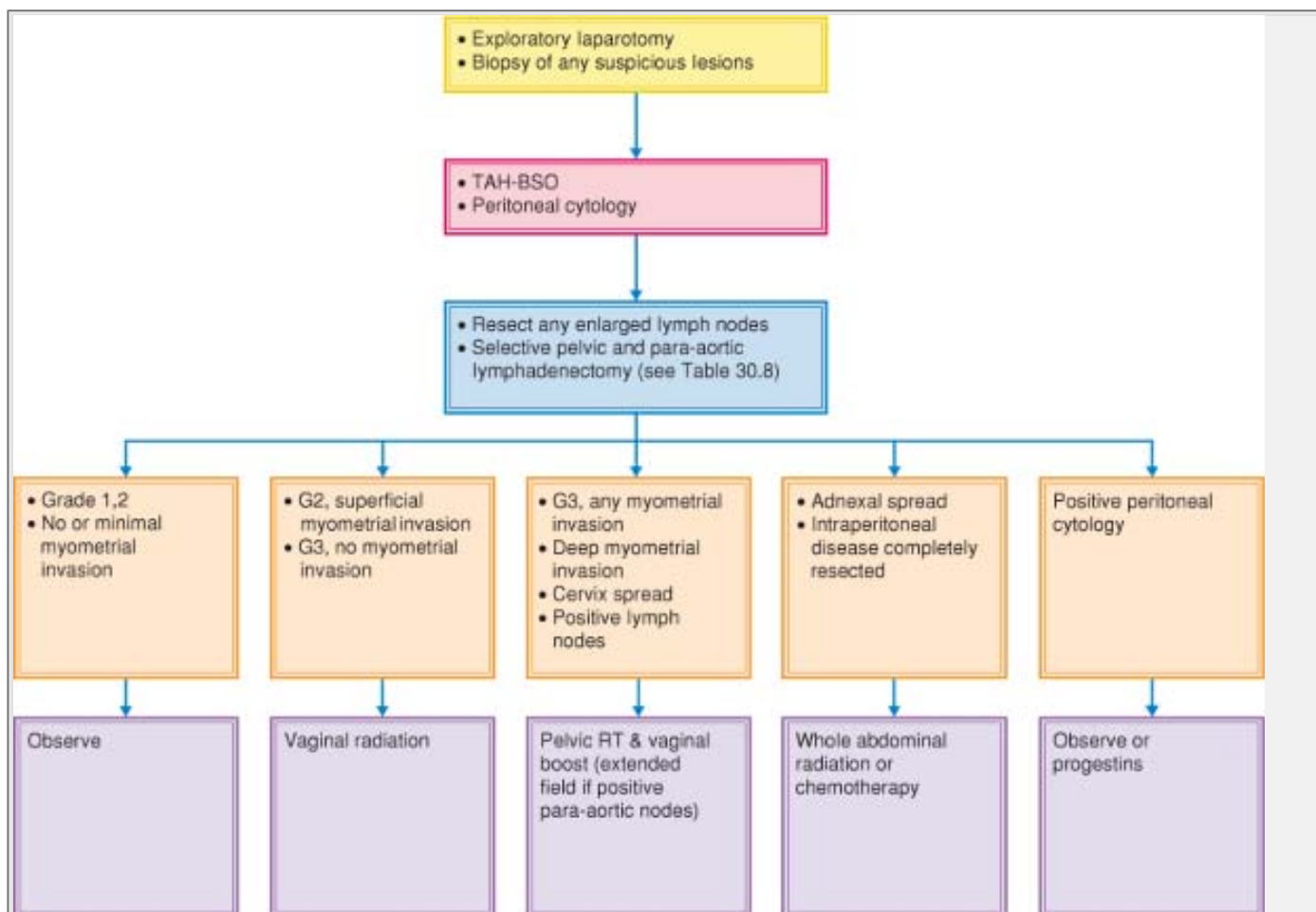


Figure 33.7 Management of patients with clinical Stage I and II endometrial carcinoma. TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; RT, radiotherapy.

Laparotomy is performed through an abdominal incision that is adequate to allow thorough intra-abdominal exploration and retroperitoneal lymph node dissection, if necessary. A lower-abdominal midline vertical incision is most commonly used, although a lower-abdominal transverse, muscle-dividing incision (e.g., Maylard incision) or muscle-detaching incision (e.g., Cherney incision) usually provides adequate exposure. After opening the

abdomen, peritoneal washings are taken from the subdiaphragmatic area, paracolic gutters, and pelvis using 50 mL of saline for each. These washings are sent to the cytology laboratory for examination. Exploration of the abdomen and pelvis is then performed, noting particularly the diaphragm, liver, omentum, and pelvic and aortic lymph nodes. The uterus should be observed for tumor on the serosal surface. Any suspicious-looking lesions or lymph nodes should be excised for biopsy or removed for histologic examination. The uterus is opened in the operating room, and tumor size, depth of myometrial invasion, and cervical extension are assessed. This information, along with the surgical findings and knowledge of the preoperative histology, influences whether pelvic and aortic lymph node dissection is indicated. The uterus is sent to the pathology laboratory, where tissue can be obtained for measurement of steroid hormone receptors and flow cytometry.

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For patients in whom lymph node sampling is indicated, lower para-aortic lymph node resection can be accomplished by extending the pelvic peritoneal incisions over the common iliac arteries and lower aorta. Samples of lymph nodes along the upper common iliac vessels are removed from either side and the fat pad overlying the vena cava. Pelvic lymph node samples are obtained by removing nodes overlying the midportion of the external iliac artery and vein and within the obturator fossa above and along the obturator nerve. An omental biopsy or partial omentectomy may also be performed.

Vaginal Hysterectomy

Vaginal hysterectomy may be considered for selected patients who are extremely obese and have a poor medical status, or for patients with extensive uterovaginal prolapse. The disadvantages to this approach are that bilateral salpingo-oophorectomy often is technically difficult and abdominal exploration and lymph node sampling cannot be performed. **Vaginal hysterectomy is, therefore, particularly suitable for patients who are at low risk for extrauterine spread of disease (i.e., those with clinical stage I, well-differentiated tumors). In one report, a 94% survival rate was found in 56 patients with clinical stage I endometrial carcinoma treated by vaginal hysterectomy, with or without postoperative radiotherapy (mostly brachytherapy).** Three fourths of these patients had grade 1 lesions (158). Others have reported similar good results (159,160,161). Vaginal hysterectomy clearly is preferable to radiation therapy alone, but generally should

be reserved for specific patients.

Laparoscopic Management

Recent advances in endoscopic surgery have allowed application of a laparoscopic approach to the management of endometrial cancer. Since 1992, **there have been several reports that have documented the feasibility of laparoscopically assisted vaginal hysterectomy with bilateral salpingo-oophorectomy and laparoscopic retroperitoneal lymph node sampling for staging and treatment of patients with endometrial cancer** (162,163,164). In an early study of 59 patients with endometrial cancer managed laparoscopically, 29 had retroperitoneal lymph node sampling (162). In a comparison study of the results of laparoscopic versus traditional laparotomy management of 44 patients with endometrial cancer, 20 patients underwent successful laparoscopic management, 15 had both pelvic and para-aortic lymph node sampling, and 4 had pelvic node sampling only. There was no difference in the number of lymph nodes (19 versus 17) removed in the laparoscopy and laparotomy groups, respectively. Patients undergoing laparoscopic management had shorter hospital stays (2.5 versus 5.0 days) and a lower overall complication rate, although all three patients who had serious complications (one ureteral injury and two small bowel herniations through 12-mm trocar sites) were in the laparoscopy group (163). A subsequent retrospective analysis compared the clinical outcomes and hospital charges for 69 women with early-stage endometrial cancer who underwent laparoscopically assisted vaginal hysterectomy, compared with 251 women who had traditional laparotomy. The patients managed laparoscopically had fewer complications, shorter hospital stays, and lower overall hospital charges than those who underwent laparotomy. Furthermore, there was no difference in recurrence rates between the two groups (164). Several other retrospective studies have evaluated the validity of laparoscopic surgery in endometrial cancer (165,166,167,168,169). In general, these studies demonstrated no differences in number of lymph nodes, estimated blood loss, and disease-free recurrence or survival with laparoscopic versus laparotomy approach to treatment, whereas decreased perioperative morbidity, longer operating times, shorter hospital stays, and earlier return to work were associated with laparoscopy compared with laparotomy. **There has been only one randomized trial published comparing laparoscopically assisted vaginal hysterectomy versus abdominal surgery in patients with endometrial cancer** (170). Seventy patients with FIGO stages I to III were randomized to laparoscopically assisted simple or radical hysterectomy versus simple or

radical abdominal hysterectomy with or without lymph node dissection. **Blood loss and transfusion rates were lower in the laparoscopy group, whereas lymph node yield, duration of surgery, and incidence of postoperative complications were similar for both groups. Overall and recurrence-free survival did not differ significantly between the two operative approaches.**

Although results of laparoscopic management of endometrial cancer are encouraging, long-term survival analysis is lacking and the risks of port-site metastasis (171), vaginal cuff recurrence (172), and higher incidence of positive peritoneal cytology (173) have been noted. The GOG is currently conducting a large, randomized trial comparing laparoscopically assisted hysterectomy and staging with standard laparotomy approach to evaluate the equivalence of these two approaches with respect to complications and outcomes.

Radical Hysterectomy

Radical hysterectomy, with removal of the parametria and upper vagina, as well as bilateral pelvic lymphadenectomy, does not improve survival of patients with clinical stage I disease compared with extrafascial hysterectomy and bilateral salpingo-oophorectomy alone (174,175,176,177). Radical hysterectomy also increases both intraoperative and postoperative morbidity and should not, therefore, be performed for treatment of apparent early endometrial cancer.

Radiation Therapy

Primary surgery followed by individualized radiation therapy has become the most widely accepted treatment for early-stage endometrial cancers. However, about 5% to 15% of endometrial cancer patients have severe medical conditions that render them unsuitable for surgery (79). These patients tend to be elderly and obese with multiple chronic or acute medical illnesses, such as hypertension, cardiac disease, diabetes mellitus, and pulmonary, renal, and neurologic diseases.

Several series have shown that radiotherapy is effective treatment for patients with inoperable endometrial cancer (178,179,180,181,182,183,184,185,186,187) (Table 33.13). One reported on the treatment of 120 patients with clinical stage I and 17

patients with clinical stage II endometrial cancer with radiation alone, 85% of whom received only intracavitary irradiation. Because of the high incidence of death caused by intercurrent illness in this group of patients, the 5- and 10-year overall survival rates were only 55% and 28%, respectively, compared with disease-specific survival rates of 87% and 85%, respectively. There was no difference in disease-specific survival rates between patients with stage I and II disease. Intrauterine cancer recurred in 14% of patients, and extrauterine pelvic disease recurred in 3%. The authors also treated 15 patients with stage III and IV disease, usually with a combination of external-beam and intracavitary radiation therapy, yielding a 5-year disease-specific survival rate of 49%. Five patients (3%) had serious late complications of radiation therapy (187).

Although it is generally agreed that intracavitary irradiation is necessary to achieve adequate local control, the indications for external-beam radiation therapy in the primary treatment of endometrial cancer are less well defined. Patients with cervical involvement and known or suspected extrauterine pelvic spread undoubtedly would benefit from external-beam radiation therapy. Theoretically, external-beam irradiation could also sterilize microscopic nodal disease and possibly increase the radiation dose to deep myometrial or subserosal uterine disease, which may receive an insufficient dose from intracavitary irradiation alone. A correlation between tumor grade and recurrence has been noted in several reports. One found that the 5-year progression-free survival rate for medically inoperable patients with clinical stage I disease treated with radiotherapy alone was 94% for grade 1, 92% for grade 2, and 78% for grade 3 tumors (184). Therefore, **patients with grade 3 tumors and a known propensity for deep myometrial invasion and lymph node metastasis also may benefit from external-beam therapy.**

Table 33.13 Review of Recent Series of Endometrial Carcinoma Treated with Radiation Alone

Authors	Year	Stage	No. of Patients	Local Recurrence Rate (%)	Disease-specific Survival Rate (%)	Major Complication Rate (%)*
Landgren et al. (178)	1976	I-II	124	22	68	7
		III-IV	26	42	22	
Abayomi et al. (179)	1982	I-II	50	26	78	15
		III-IV	16		10	
Patanaphan et al. (180)	1985	I-II	42	14	64	2
		III-IV	10	60	20	
Jones and Stout (181)	1986	I-II	146	22	61	4
		III-IV	14	79	14	
Varia et al. (182)	1987	I-II	73	21	43	10
Wang et al. (183)	1987	I-II	41	22	76	5
Grigsby et al. (184)	1987	I	69	9	88	16
Taghian et al. (185)	1988	I-II	94	6	70	17
		III-IV	10	10	27	
Lehoczky et al. (186)	1991	I	171	20	75	0
Kupelian et al. (187)	1993	I-II	137	14	85	3
		III-IV	15	32	49	

*For all stages combined.

From **Kupelian PA, Eifel PJ, Tornos C, et al.** Treatment of endometrial carcinoma with radiation therapy alone. *Int J Radiat Oncol Biol Phys* 1993;27:817-824, with permission.

The decision to treat a patient who has endometrial cancer with radiation alone must involve a careful analysis of the relative risks and benefits of surgery. Although radiation alone can produce excellent survival and local control, it should be considered for definitive treatment only if the operative risk is estimated to exceed the 10% to 15% risk for uterine recurrence expected with radiation treatment alone.

Postoperative Adjuvant Therapy

Postoperative therapy should be based on prognostic factors determined by surgical

and pathologic staging. Patients can generally be classified into three treatment categories (Table 33.14).:

- **Low Risk Patients who show a low incidence of recurrence and a high rate of cure without any postoperative therapy**
- **Intermediate Risk Patients who have a reduced rate of surgical cure but may or may not benefit from additional therapy**
- **High Risk Patients who have a high rate of recurrence and a low survival rate without postoperative therapy**

Options for postoperative management in these patients include observation, vaginal vault irradiation, external pelvic irradiation, extended-field (pelvic and para-aortic) irradiation, whole-abdomen irradiation, progestins, or systemic chemotherapy (see Fig. 33.7).

Observation

Patients with grade 1 and 2 lesions without myometrial invasion (stage Ia, grades 1 and 2) have an excellent prognosis and require no postoperative therapy. In a GOG

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study, there were no recurrences and a 100% disease-free 5-year survival rate in the 91 patients in this category, 72 of whom had received no additional treatment after hysterectomy (88). Other investigators have reported equally favorable results with only surgical therapy in similar patients (188,189).

Table 33.14 Postoperative Management of Endometrial Carcinoma Based on Surgical-Pathologic Findings and Stage

<i>Surgical-Pathologic Findings</i>	<i>Stage</i>	<i>Postoperative Treatment</i>
Low risk		
G1, G2, no myoinvasion No cervix/isthmus invasion Negative peritoneal cytology No LVSI No evidence of metastasis	Ia G1, 2	None
Intermediate risk		
G1, G2, <50% myoinvasion G3, no myoinvasion	Ib G1, 2 Ia G3	Vaginal cuff irradiation
G3, <50% myoinvasion G1, G2 isthmus/cervix extension	Ib G3 IIa G1, G2	Pelvic versus vaginal cuff irradiation
G1, G2, G3 >50% myoinvasion G3, isthmus/cervix extension G1, G2, G3 cervix invasion LVSI	Ic G1, G2, G3 IIa G3 IIb G1, G2, G3	Pelvic irradiation plus vaginal cuff boost
Positive peritoneal cytology	IIIa (+1 cytology)	Progestin
High risk		
Adnexal/serosal/parametrial spread Vaginal metastasis	IIIa G1, G2, G3 IIIb G1, G2, G3	Pelvic and vaginal irradiation (Extended-field radiation therapy if positive aortic/ common iliac lymph nodes)
Lymph node metastasis	IIIc G1, G2, G3	
Bladder/rectal invasion Intraperitoneal spread	IVa IVb	Pelvic and vaginal irradiation Whole-abdomen irradiation; systemic chemotherapy
LVSI, lymph-vascular space invasion.		

Vaginal Vault Irradiation

Numerous studies have shown that the incidence of vaginal recurrence in patients with tumors apparently confined to the uterus can be reduced from as high as 15% to 1% or 2% by the administration of vaginal irradiation. This finding is important because vaginal vault recurrence carries a poor prognosis (190,191). Preoperative or

postoperative vaginal vault irradiation use has been found to decrease the incidence of vaginal recurrence from 14% to 1.7% and to improve 5-year survival rates from 75% to over 90% (99,192). In a 10-year follow-up of a randomized trial comparing surgery alone (total abdominal hysterectomy and bilateral salpingo-oophorectomy) with preoperative and postoperative radium treatment in patients with clinical stage I endometrial adenocarcinoma, the incidence of vaginal recurrence was 7.5% with hysterectomy alone, 4.5% with preoperative intracavitary radium followed by hysterectomy, and 0% with hysterectomy followed by postoperative vaginal radium (193). In a subsequent study of 92 patients with surgical stage I disease who had grade 1 or 2 tumors with less than 50% myometrial invasion treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy and postoperative vaginal cesium or radium, there were no recurrences, and the 5-year estimated disease-free survival rate was 99%. There was only one minor complication, proctitis, which responded to conservative treatment (194).

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In a GOG study of surgical and pathologic risk factors and outcomes, none of the three recurrences in the vaginal radiation implant group was vaginal or pelvic, whereas 7.4% of recurrences in the pelvic radiation therapy group were vaginal, and 18.2% of recurrences were vaginal in the group that did not receive adjuvant radiation. The investigators concluded that postoperative vaginal cuff irradiation reduced local recurrence and had a therapeutic ratio superior to whole-pelvis irradiation in patients at risk for isolated vaginal cuff recurrence (88).

In the past, postoperative vaginal irradiation was most commonly administered using low-dose-rate radium or cesium sources via colpostats to deliver a surface dose of 6,000 to 7,000 cGy to the upper vagina. More recently, afterloading outpatient techniques using high-dose-rate iridium sources have been employed (195,196,197,198,199). Morbidity is low, although vaginal stenosis and dyspareunia may be a problem for postmenopausal patients in the absence of regular vaginal dilation. **Patients most likely to benefit from vaginal irradiation are those who have surgical stage I grade 1 and 2 tumors with superficial (less than 50%) myometrial invasion (stage Ib G1,2) or grade 3 tumors with no invasion (stage Ia G3) and patients with stage IIa G1,2 disease with superficial myometrial invasion.**

External Pelvic Irradiation

External pelvic irradiation decreases the risk of pelvic recurrence after hysterectomy in certain high-risk groups. Patients found to benefit most from adjuvant

postoperative whole-pelvis irradiation are those with cervical involvement, pelvic lymph node metastases, or pelvic disease outside the uterus (adnexa, parametria), and patients with clinical stage I disease who are at significant risk for nodal metastasis (grade 3 tumors with any degree of myometrial invasion, grade 1 and 2 tumors with more than 50% myometrial invasion, large [>2 cm] grade 2 and 3 tumors with superficial myometrial invasion, and any grade tumor with LVSI) (200).

In a study of 41 endometrial cancer patients treated with postoperative pelvic irradiation (5,000-5,040 cGy) who had grade 3 tumors or deep myometrial invasion and histologically negative para-aortic lymph nodes (pelvic lymph nodes not sampled), 4 patients (9.7%) developed recurrences. Only one of the recurrences (2.4%) was within the treatment field, however, and the 5-year estimated disease-free survival rate was 88% (194). In the GOG study, the pelvic recurrence rate was higher in the surgery-only group of patients (31.8%) than in the patients who received postoperative external beam radiation therapy (16.8%) (88).

In 1980, the first randomized study was performed to evaluate the possible benefit of postoperative pelvic irradiation in clinical stage I endometrial cancer (105). After total abdominal hysterectomy and bilateral salpingo-oophorectomy, all 540 patients received vaginal vault radium and were then randomized to receive either 4,000 cGy of whole-pelvis irradiation or no further therapy. The addition of pelvic irradiation did not affect the overall 5-year survival rate. Patients receiving pelvic irradiation had a lower pelvic failure rate but a higher distant failure rate. Of note, patients with grade 3 tumors and more than 50% myometrial invasion had a lower rate of death from cancer if they received postoperative pelvic irradiation (18.2% versus 27.5%). This study has been criticized for a lack of complete surgical staging (no lymph node biopsies were performed) and the relatively low dose of external-beam irradiation (4,000 cGy) used.

The GOG recently published a prospective, randomized study of surgery alone versus surgery plus adjuvant pelvic irradiation in intermediate-risk endometrial cancer (stages Ib to IIb occult). Of 392 patients accrued to the study, more than 80% were actually low-risk patients (90.6% stage I, 81.6% grade 1-2, 82% $<50\%$ myometrial invasion). **Disease recurrence was reduced by 58% ($p=0.007$) with the use of postoperative pelvic irradiation.** After 2 years, the cumulative recurrence rate was 12% in the group with no postoperative treatment compared with 3% in the group that received pelvic irradiation. The pelvic failure rate was 8.9% in the surgery-alone group compared with 1.6% in the postoperative pelvic irradiation group. **Overall survival rates also were improved,**

although not significantly, in patients receiving postoperative pelvic irradiation compared with those treated only with surgery (92% versus 86%, respectively) (201).

Another randomized trial of surgery and postoperative pelvic radiotherapy versus surgery alone for 714 patients with stage I endometrial carcinoma was carried out by the Netherlands PORTEC Study Group. Eligibility criteria were stage IC, grade 1 to 2, and stage IB, grade 2 to 3; patients with stage IB, grade 3, made up only 10% of the study population, and lymph node biopsies and peritoneal cytology were not required. **Local-regional recurrences developed in 14% of the surgery group, compared with 4% of the postoperative pelvic irradiation group. Overall, the 5-year survival rate was no different between the two groups (85% versus 81%, respectively) (202).**

Postoperative whole-pelvis external-beam irradiation usually involves the delivery of 4,500 to 5,040 cGy in 180 cGy daily fractions over 5 to 6 weeks to a field encompassing the upper one half of the vagina inferiorly, the lower border of the L4 vertebral body superiorly, and 1 cm lateral to the margins of the bony pelvis. The dose of radiation at the surface of the vaginal apex usually is boosted to 6,000 to 7,000 cGy by a variety of techniques. The most frequently reported side effects are gastrointestinal, usually abdominal cramps and diarrhea, although more serious complications such as bleeding, proctitis, bowel obstruction, and fistula can occur and may require surgical correction. The urinary system may also be affected in the form of hematuria, cystitis, or fistula. The overall complication rate ranges from 25% to 40%; however, the rate of serious complications requiring surgical intervention is about 1.5% to 3%.

Patients at high risk for recurrence may benefit from pelvic irradiation. The pelvic failure rate is reduced and, at least in patients with grade 3 tumors and deep myometrial invasion, survival rates also appear to be improved. Patients with cervical extension and extrauterine pelvic disease, including adnexal spread, parametrial involvement, and pelvic lymph node metastases, in the absence of extrapelvic disease, also should benefit from postoperative pelvic irradiation.

Extended-field Irradiation

Patients with histologically proven para-aortic node metastases who have no other evidence of disease spread outside the pelvis should be treated with extended-field irradiation. The entire pelvis, common iliac lymph nodes, and para-aortic lymph nodes are included within the radiation field. The para-aortic radiation dose is limited to 4,500 to 5,000 cGy. **Extended-**

field radiotherapy appears to improve survival in patients with endometrial cancer who have positive para-aortic lymph nodes (88,203,204,205,206).

Five-year survival rates of 47% and 43% have been reported for patients with surgically confirmed para-aortic lymph node metastases only and for those with para-aortic as well as pelvic lymph node metastases, respectively, using postoperative extended-field irradiation. Only one case of severe enteric morbidity occurred in 48 patients, a complication rate of 2% (203). In a GOG study, 37 of 48 patients with positive para-aortic nodes received postoperative para-aortic irradiation, 36% of whom remained tumor free at 5 years (88). A comparison of patients with positive para-aortic nodes treated with *megestrol acetate* alone versus *megestrol acetate* and extended-field irradiation showed that the survival rate in the patients receiving extended-field irradiation was significantly better: 53% versus 12.5%, respectively (204). In another study of 18 patients with positive para-aortic nodes, 5-year survival rates were 67% for microscopic nodal disease and 17% for gross nodal disease (205).

Whole-abdomen Irradiation

Whole-abdomen irradiation therapy usually is reserved for patients with stage III and IV endometrial cancer. It may also be considered for patients who have papillary serous or mixed mllerian tumors, which have a propensity for upper-abdominal

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recurrence (207,208,209,210,211,212). The recommended dose to the whole abdomen is 3,000 cGy in 20 daily fractions of 150 cGy, with kidney shielding at 1,500 to 2,000 cGy, along with an additional 1,500 cGy to the para-aortic lymph nodes and 2,000 cGy to the pelvis. Gastrointestinal side effects, including nausea, vomiting and diarrhea, sometimes make it necessary to interrupt therapy, but it is rare for patients to discontinue treatment because of these symptoms. Hematologic toxicity can be expected to occur during whole-abdomen irradiation, but it is usually mild. The incidence of late complications, mainly chronic diarrhea and small bowel obstruction, generally is low (5% to 10%).

In a series of 27 patients treated with surgical stage III endometrial cancer with whole-abdomen irradiation, patients with spread to the adnexa, positive peritoneal cytology, or both had a 5-year, relapse-free survival of 90%, whereas all patients with macroscopic disease beyond the adnexa had recurrence (207). Similar results were reported by others (208,209). Some have advocated the use of adjuvant whole-abdomen radiotherapy for patients with high-risk stage

I and II endometrial carcinoma, including those with deep myometrial invasion, high-grade tumors, and papillary serous histology, because of the high proportion of recurrences in the upper abdomen. A 5-year recurrence-free survival rate of 85% has been reported (210,211). With whole-abdomen irradiation in patients at increased risk for intra-abdominal metastatic disease, such as those with nonnodal extrauterine disease and papillary serous histology, an actuarial 5-year relapse-free survival rate of 70% has been reported, with no significant toxicity (212). Similarly, others have noted a 3-year disease-free survival rate of 79% in patients with stage III and IV endometrial adenocarcinoma treated with whole-abdomen irradiation (213). Still other reports of using adjuvant postoperative whole-abdomen irradiation in early-stage uterine papillary serous carcinoma suggest a reduction in recurrence rates (214,215,216). Unfortunately, most recurrences are in the upper abdomen in all of these patients, despite this type of radiotherapy. **It is reasonable to use whole-abdomen irradiation postoperatively to treat patients with adnexal or upper-abdominal disease, such as in the omentum, that has been completely excised and in patients who are at very high risk for intra-abdominal recurrence, such as those with papillary serous tumors. It should not be used in patients with gross residual intraperitoneal disease.**

Progestins

Because most endometrial cancers have both estrogen and progesterone receptors and progestins have been successfully used to treat metastatic endometrial cancer, postoperative adjuvant progestin therapy has been attempted to reduce the risk of recurrence. This therapy is attractive because it provides systemic treatment and has few side effects. Unfortunately, **several large randomized, placebo-controlled studies have failed to identify a benefit for adjuvant progestin therapy** (217,218,219,220,221,222).

Conversely, in a series of 25 patients with positive peritoneal cytology as their only evidence of disease spread outside the uterus who were treated with adjuvant progestin for 1 year postoperatively (223), 22 patients had a second-look laparoscopy, and only one patient was found to have persistent intraperitoneal malignant cells. No patient had evidence of recurrent cancer. Therefore, progestins may have a role in treating positive peritoneal cytology in this setting (224).

Chemotherapy

Adjuvant cytotoxic chemotherapy has been studied in a few trials. The GOG treated 181 patients who had poor prognostic factors with postoperative irradiation and then randomly assigned patients to receive no further therapy or *doxorubicin* (*Adriamycin*) chemotherapy. After 5 years of observation, there was no difference in recurrence rates between the two groups (225). Researchers at the M. D. Anderson Cancer Center treated 62 high-risk patients with postoperative adjuvant *cisplatin*, *doxorubicin*, and *cyclophosphamide* (PAC) chemotherapy. The presence of extrauterine disease was the only significant risk factor for recurrence, and no benefit to adjuvant chemotherapy could be found (226,227).

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More recently, use of adjuvant postoperative chemotherapy has been studied in patients with surgical stage III/IV disease. **The GOG compared whole-abdomen irradiation versus *doxorubicin/cisplatin* chemotherapy in 388 patients with advanced endometrial cancer who had undergone maximal surgical resection of disease to less than 2cm. Patients who received chemotherapy had a 13% improvement in 2-year progression-free survival (50% versus 46%) and an 11% improvement in overall 2-year survival (70% versus 59%) compared with patients treated with whole-abdomen irradiation.** Although this study was the first to suggest an improvement in outcome for use of adjuvant chemotherapy compared with radiation, toxicity was more prevalent with chemotherapy; patients with gross residual disease were assigned to the radiation arm, almost guaranteeing failure; and overall, 55% of patients experienced a recurrence or progression during the study period (228).

Clinical Stage II

Endometrial cancer involving the cervix either contiguously or by lymphatic spread has a poorer prognosis than disease confined to the corpus

(229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247).

Preoperative assessment of cervical involvement is difficult. **Endocervical curettage has relatively high false-positive (50%-80%) and false-negative rates.** Histologic proof of cancer infiltration of the cervix or presence of obvious tumor on the cervix is the only reliable means of diagnosing cervical involvement, although ultrasonography, hysteroscopy, or MRI may show cervical invasion.

The relatively small number of true stage II cases in reported series and the lack of

randomized, prospective studies preclude formulation of a definitive treatment plan. **Three areas must be addressed in any treatment plan:**

- **For optimal results, the uterus should be removed in all patients.**
- **Because the incidence of pelvic lymph node metastases is about 36% in stage II endometrial cancer, any treatment protocol should include treatment of these lymph nodes.**
- **Because the incidence of disease spread outside the pelvis to the para-aortic lymph nodes, adnexal structures, and upper abdomen is higher than in stage I disease, attention should be directed to evaluating and treating extrapelvic disease.**

Two approaches have usually been used in the treatment of clinical stage II disease:

- **Radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy**
- **Combined radiation and surgery (external pelvic irradiation and intracavitary radium or cesium followed in 6 weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy)**

An initial radical surgical approach to treatment of clinical stage II endometrial cancer has the advantage of allowing accurate surgical—pathologic information to be obtained. Conversely, many patients with endometrial cancer are elderly and obese and have medical problems that make this approach unsuitable. In addition, reported results are no better than those with combined radiation and less radical surgical therapy (247). The use of radical hysterectomy may be limited to patients with anatomic problems that prevent optimum dosimetry or other conditions that conflict with the use of radiation therapy.

The most common, **traditional approach to the management of clinical stage II endometrial cancer has been to use external and intracavitary irradiation followed by**

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extrafascial hysterectomy. This combined approach has resulted in 5-year survival rates of 60% to 80%, with severe gastrointestinal or urologic complications occurring in about 10% of patients (230,231,232,233,234,235,236,237,238). Patients who have medically inoperable disease are usually treated with external-beam irradiation and one or two intracavitary insertions. Compared with combined radiation and surgery, the results with radiation alone are diminished, but about 50% of patients are long-term survivors (187) (see Table 33.13).

Another method of management of clinical stage II endometrial cancer that is gaining favor is an initial surgical approach followed by irradiation. This method is based on the difficulty in establishing the preoperative diagnosis of cervical involvement in the absence of a gross cervical tumor, the evidence that radiation is equally effective when given after hysterectomy, and the high incidence of extrapelvic disease when the cervix is involved. Exploratory laparotomy with an extrafascial or modified radical hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings for cytology, resection of grossly enlarged pelvic nodes, and selective high common iliac and lower para-aortic lymphadenectomy are performed. These procedures are followed by appropriate pelvic or extended-field external and intravaginal irradiation, depending on the results of surgical staging. Excellent results have been reported using this treatment scheme (241,242,243,244).

Clinical Stages III and IV

Clinical stage III disease accounts for about 7% to 10% of all endometrial carcinomas (248,249,250,251,252,253,254,255). Patients usually have clinical evidence of disease spread to the parametria, pelvic sidewall, or adnexal structures; less frequently, there is spread to the vagina or pelvic peritoneum. **Treatment for stage III endometrial carcinoma must be individualized, but initial operative evaluation and treatment should be considered because of the high risk for occult lymph node metastases and intraperitoneal spread when disease is known to extend outside of the uterus into the pelvis.** In the presence of an adnexal mass, surgery should be performed initially to determine the nature of the mass. Surgery should also be performed to determine the extent of disease and to remove the bulk of the disease if possible. This procedure should include peritoneal washings for cytologic examination, selective para-aortic and pelvic

lymphadenectomy, removal of any enlarged lymph nodes, biopsy or excision of any suspicious areas within the peritoneal cavity, and partial omentectomy and peritoneal biopsies. Except in patients with bulky parametrial disease, total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed. **The goal of surgery is eradication of all macroscopic disease because this finding is of major prognostic importance in the management of patients with clinical stage III disease.** Postoperative therapy can then be tailored to the extent of disease.

Results of therapy depend on the extent and nature of disease. A 5-year survival rate of 54% has been reported for all patients with stage III disease; however, the survival was 80% when only adnexal metastases were present, compared with 15% when other extrauterine pelvic structures were involved (248). Patients with surgical—pathologic stage III disease have a much better survival rate (40%) than those with clinical stage III disease (16%) (237). Patients who are treated with combined surgery and irradiation fare better than patients who receive radiation therapy alone (255).

Stage IV endometrial adenocarcinoma, in which tumor invades the bladder or rectum or extends outside the pelvis, makes up about 3% of cases (255,256,257,258,259). **Treatment of stage IV disease is patient dependent but usually involves a combination of surgery, radiation therapy, and systemic hormonal therapy or chemotherapy.** One objective of surgery and radiation therapy is to achieve local disease control in the pelvis to provide palliative relief of bleeding, discharge, and complications involving the bladder and rectum. In one report, control of pelvic disease was achieved in 28% of 72 patients with stage IV disease treated with radiation alone or in combination with surgery, progestins, or both (256). **Several reports have noted a positive impact of cytoreductive surgery on survival, the median**

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survival being about 3 times greater with optimal cytoreduction (18–34 months versus 8–11 months, respectively) (257,258,259). Pelvic exenteration may be considered in the very rare patient in whom disease is limited to the bladder, rectum, or both (260,261).

Recurrent Disease

About one fourth of patients treated for early endometrial cancer develop recurrent disease. More than one half of the recurrences develop within 2 years, and about three fourths occur within 3 years of initial treatment. The distribution

of recurrences is dependent in large part on the type of primary therapy: surgery alone versus surgery plus local or regional radiotherapy. In a GOG study of 390 patients with surgical stage I disease, vaginal and pelvic recurrences were noted to make up 53% of all recurrences in the group treated with surgery alone, whereas only 30% of recurrences were vaginal or pelvic in the group treated with combined surgery and radiotherapy (88). Therefore, after combined surgery and radiotherapy (vaginal or external beam), 70% or more of patients with treatment failures have distant metastases, and most of these patients do not have evidence of local or pelvic recurrence. The most common sites of extrapelvic metastases are the lung, abdomen, lymph nodes (aortic, supraclavicular, inguinal), liver, brain, and bone. In general, patients with isolated vaginal recurrences fare better than those with pelvic recurrences, who in turn have a better chance of cure than those with distant metastases. Patients who initially have well-differentiated tumors or who develop recurrent cancer more than 3 years after the primary therapy also tend to have an improved prognosis.

In a 1984 report on 379 patients with recurrent endometrial cancer seen at the Norwegian Radium Hospital from 1960 to 1976 (262), site of recurrence was local or regional in 190 patients (50%), distant in 108 patients (28%), and local and distant in 81 patients (21%). The median time of recurrence was 14 months for patients with local recurrences and 19 months for patients with distant metastases. Of all recurrences, 34% were detected within 1 year, and 76% were detected within 3 years of primary treatment. At the time of diagnosis of recurrence, 32% of patients had no symptoms. **Vaginal bleeding was the most common symptom associated with local recurrence, and pelvic pain was most often present with pelvic recurrence.** Hemoptysis was the initial symptom in 32% of patients with lung metastases, but 45% of cases of lung metastases were asymptomatic and picked up on routine chest x-ray. Only 9% of patients with metastases at other sites did not have symptoms; most had pain (37%) or other symptoms such as anorexia, nausea and vomiting, or ascites related to intra-abdominal carcinomatosis, neurologic symptoms such as seizures from brain metastases, or jaundice caused by liver metastases.

Overall, only 29 (7.7%) of the 379 patients were alive without evidence of disease from 3 to 19 years. This included 22 patients (12%) with local or pelvic recurrence, 5 patients (5%) with distant metastases, and 2 patients (2%) with both local and distant recurrences. The best results were obtained in the 42 patients with vaginal vault recurrences who were treated with radiotherapy, resulting in a 24% survival rate. None of the 78 patients with pelvic soft tissue recurrence survived. Three patients (7%) with only lung metastases treated with progestins, two patients with lymph node metastases treated with combined radiotherapy and progestins, and two patients with local recurrence and lung metastases treated

with radiotherapy, surgery, and progestins survived.

Surgery

A small subset of patients who develop recurrent endometrial cancer may benefit from surgical intervention. Pelvic or vaginal recurrence in patients who have not received prior pelvic irradiation is best treated with external irradiation plus some type of brachytherapy. Surgical resection of a metastatic nodule greater than 2 cm in diameter before irradiation, however, may improve local control. Pretherapy investigation for extrapelvic metastasis in these patients may include surgical evaluation of the peritoneal cavity and retroperitoneal lymph nodes for evidence of subclinical metastases.

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In one small series, upper-abdominal disease was found at laparotomy in 3 (37.5%) of 8 patients with presumed localized pelvic recurrence. Presence of subclinical extrapelvic metastases was associated with larger pelvic tumor size (>2 cm) and elevated serum CA125 levels (263). A few patients with intraperitoneal recurrence may benefit from laparotomy to relieve intestinal obstruction. Tumor-reductive surgery may be performed before administration of whole-abdomen radiation therapy or systemic hormonal therapy or chemotherapy.

Isolated central pelvic recurrence after irradiation is rare. In patients with this type of recurrence, exploratory laparotomy may be performed with the plan to proceed with pelvic exenteration if there is no evidence of disease outside the pelvis and no lymph node metastases. Exenterative surgery for recurrent endometrial cancer in the pelvis is of value in selected patients because of the high incidence of associated occult extrapelvic metastases. Of 36 patients who underwent pelvic exenteration for recurrent endometrial carcinoma at Memorial Sloan-Kettering Cancer Center, 75% died of their cancer within 1 year of operation, and only 14% were alive after 5 years (261).

Radiation Therapy

Patients with isolated local or regional recurrences after initial surgical treatment of endometrial cancer should be treated with radiotherapy (191,264-271). The best local control and subsequent cure are usually achieved by a combination of external-beam radiation therapy followed by a brachytherapy boost to deliver a total tumor dose of at least 6,000 cGy. Women with low-volume disease limited to the pelvis have the best outcome.

For patients with isolated vaginal recurrence treated with irradiation, reported survival rates range from 24% to 45%. Conversely, for those patients who undergo irradiation of the pelvic extension of their disease, lower survival rates (0%-24%) have been reported. Significant factors that determine control of pelvic disease and survival in patients with locally recurrent endometrial cancer include initial endometrial cancer grade 1, younger age at recurrence, recurrent tumor size 2 cm or less, time from initial treatment to recurrence of more than 1 year, vaginal versus pelvic disease, and radiation therapy that included brachytherapy vaginal boost.

Hormone Therapy

The use of progestational agents for treatment of metastatic endometrial cancer was first described in 1961, when researchers observed an objective response rate of 29% in 21 patients (272). In a report from 1974, a beneficial response was observed in 35% of 308 patients (273). Subsequent reports have noted somewhat less optimistic response rates, probably as a result of more strictly applied criteria for objective responses (274,275,276,277) (Table 33.15). Reports from Roswell Park Cancer Center and the Mayo Clinic observed objective response rates of 16% and 11%, respectively, with an additional 15% to 40% of patients exhibiting stable disease for at least 3 months (274,275). In 1986 the GOG

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initially reported on the use of oral *medroxyprogesterone acetate* for treatment of patients with advanced or recurrent endometrial cancer (276). Of 219 patients with measurable disease, 8% had a complete response, 6% had a partial response, 52% had stable disease, and 34% developed progressive disease within 1 month.

The mean survival time for the entire group was 10.4 months. In a follow-up study comparing two different doses of oral *medroxyprogesterone acetate*, similar response rates were achieved (26% for 200 mg/day and 18% for 1,000 mg/day) (277). The type, dose, and route of administration of the progestin seemed to have no effect on response in these studies.

Table 33.15 Response to Progestin Therapy in Advanced or Recurrent Endometrial Cancer

<i>Study</i>	<i>Progestin</i>	<i>No. of Patients</i>	<i>Response Rate (%)</i>	
Piver et al. (274)	<i>HPC</i>	1,000 mg/wk IM	51	14
	<i>MPA</i>	1,000 mg/wk IM	37	19
Podratz et al. (275)	<i>HPC</i>	1-3 g/wk IM	33	9
	<i>MA</i>	320 mg/d PO	81	11
Thigpen et al. (276,277)	<i>MPA</i>	150 mg/d PO	219	14
		200 mg/d PO	138	26
		1,000 mg/d PO	140	18

HPC, hydroxyprogesterone caproate (Delalutin); MPA, medroxyprogesterone acetate (Provera, Depo-Provera); MA, megestrol acetate (Megace); IM, intramuscular; PO, oral.

The response of metastatic endometrial carcinoma to progestin therapy is related to several clinical and pathologic factors. **Higher response rates are observed in well-differentiated tumors.** A 20.5% response in low-grade tumors and only 1.4% response in high-grade tumors have been noted (275). Likewise, the probability of an objective response to progestin therapy is about 70% for tumors that are estrogen- and progesterone-receptor positive, compared with about 5% to 15% for tumors that are negative for both receptors. A longer disease-free interval is associated with higher response rates to progestins. The response rate to progestins has been found to range from 6% in patients with an interval from primary treatment to recurrence of less than 6 months to 65% in patients in whom disease recurred more than 5 years after initial treatment (274). Other observed but less well-documented factors that may have an adverse effect on response to progestins are disease recurrence within a prior radiation field, large tumor burden, and advanced primary versus recurrent disease (274,275).

Tamoxifen, a nonsteroidal antiestrogen with some estrogenic properties, has been evaluated for treatment of metastatic endometrial carcinoma based on experience in using this agent in breast cancer treatment. Its use as either a single agent or in combination with a progestin is related to its ability to inhibit the binding of estradiol to the estrogen receptor and to increase progesterone receptors. **In a review of eight studies using *tamoxifen*, 20 to 40 mg/day, in patients with metastatic endometrial carcinoma, the overall response rate was 22%, with a range of 0% to 53% (278). Responses to *tamoxifen* were more likely to be observed in patients with low-grade, hormone receptor–positive tumors who had**

a prior response to progestin therapy. In an attempt to reverse the hormone receptor downregulation seen with progestin therapy, *tamoxifen* has been given along with progestins, but the overall responses to combined *tamoxifen* and progestin therapy have been similar to those noted for single-agent progestin therapy.

Progestins are currently recommended as initial treatment for all patients with recurrent endometrioid tumors with hormone receptor-positive tumors. Radiation therapy, surgery, or both should be used whenever feasible for treatment of localized recurrent cancer such as vaginal, pelvic, bone, and peripheral lymph node disease; however, these patients should also be given long-term progestin therapy unless they are known to have a progesterone-receptor—negative tumor. Patients with nonlocalized recurrent tumors, especially if progesterone receptors are known to be positive, are candidates for progestin therapy, either *megestrol acetate*, 80 mg twice daily, or *medroxyprogesterone acetate*, 50 to 100 mg three times daily. Progestin therapy should be continued for at least 2 to 3 months before assessing response. **If a response is obtained, the progestin should be continued for as long as the disease is static or in remission. In the presence of a relative contraindication to high-dose progestin therapy (e.g., prior or current thromboembolic disease, severe heart disease, or inability of the patient to tolerate progestin therapy), *tamoxifen*, 20 mg twice daily, is recommended.** Failure to respond to hormonal therapy is an indication for initiating chemotherapy.

Chemotherapy

Although several chemotherapeutic agents or combinations of agents are capable of inducing objective responses and even remissions in patients with metastatic endometrial carcinoma, response and survival times are short, and all cytotoxic therapy should be

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considered palliative (278,279,280). The most active chemotherapeutic agents are *doxorubicin*, the *platinum* compounds *cisplatin* and *carboplatin*, and *paclitaxel* (*Taxol*). *Doxorubicin*, 50 to 60 mg/m² every 3 weeks (281,282,283); *cisplatin*, 60 to 75 mg/m² every 3 weeks (284,285); and *carboplatin*, 350 to 400 mg/m² every 4 weeks (286,287) have been associated with response rates of 21% to 29%. *Paclitaxel*, 250 mg/m² as a 24-hour infusion with granulocyte colony-stimulating factor support (287), or 175 mg/m² as a 3-hour infusion every 3 weeks (288,289,290), has produced response rates of about 36%. Alkylating agents such as *cyclophosphamide* and *melphalan*, *fluorouracil*, *altretamine* (*hexamethylmelamine*)

(291), *liposomal doxorubicin* (292), and *topotecan* (293,294) have shown activity against endometrial cancer. Most responses obtained with use of these agents have been partial, generally averaging only 3 to 6 months, with the median survival time ranging from 4 to 8 months.

Combination chemotherapy regimens employing *doxorubicin* and *cisplatin* (283,295); *cyclophosphamide*, *doxorubicin*, and *cisplatin* (296,297); *paclitaxel* and *cisplatin* with or without *doxorubicin* (298,299); and *carboplatin* and *paclitaxel* (300) have resulted in response rates ranging from 38% to 76%. Despite these fairly impressive response rates, most responses have been partial, with durations of 4 to 8 months, and the median survival time has generally been less than 12 months.

Response to chemotherapy in patients with metastatic endometrial cancer does not appear to be affected by prior or concurrent progestin therapy. Metastatic site, age, disease-free interval, histology, and tumor grade also appear to have no effect on chemotherapy response. However, patients with long disease-free intervals and better performance status may live longer.

Treatment Results

Comprehensive survival data for endometrial cancer are provided by FIGO (301). Survival in relation to clinical and surgical stage is shown in Table 33.16 and in relation to surgical stage and grade in Table 33.17. **The overall 5-year survival rate was 76%. Patients who underwent surgical staging had much better 5-year survival rates than those staged clinically across all stages** (respectively): stage I, 87% versus 54%; stage II, 76% versus

41%; stage III, 57% versus 23%; stage IV, 18% versus 12%. Survival in surgical stage I disease ranged from more than 90% for stage Ia grades 1 and 2 and stage Ib grades 1 and 2 to 63% for stage Ic grade 3.

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Table 33.16 Carcinoma of the Endometrium: Stage Distribution and Actuarial Survival by Stage (Surgical and Clinical)

Stage	Patients Treated		Survival	
	No.	%	3-Year	5-Year
Surgical				
I	3,996	70	92	87
II	709	12	82	76
III	758	13	66	59
IV	231	4	23	18
Clinical				
I	232	61	63	54
II	64	16	53	41
III	54	14	30	23
IV	33	8	12	12
Total	6,260	100	82	76

Adapted from **Creasman WT, Odicino F, Maisonneuve P, et al.**

Carcinoma of the corpus uteri. FIGO Annual Report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45-86, with permission.

Table 33.17 Surgically Staged Endometrial Cancer: Actuarial 5-Year Survival Rate (%) by Histologic Grade and Stage

Stage	Grade		
	1	2	3
Ia	93	90	69
Ib	90	93	84
Ic	89	81	63
IIa	91	78	57
IIb	78	75	58
IIIa	79	69	44
IIIb	77	40	21
IIIc	61	61	44
IVa	—	—	19
IVb	35	27	7

Adapted from **Creasman WT, Odicino F, Maisonneuve P, et al.** Carcinoma of the corpus uteri. FIGO Annual Report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 2001;6:45-86, with permission.

Follow-up after Treatment

History and physical examination remain the most effective methods of follow-up in patients treated for endometrial cancer (302,303,304,305). **Patients should be examined every 3 to 4 months during the first 2 years and every 6 months thereafter. About one half of patients discovered to have recurrent cancer have symptoms, and 75% to 80% of recurrences are detected initially on physical examination. Particular attention should be given to peripheral lymph nodes, the abdomen, and the pelvis.** Very few asymptomatic recurrences are detected by vaginal cytology.

Chest x-ray every 12 months is an important method of posttreatment surveillance. **Almost one half of all asymptomatic recurrences are detected by chest x-ray.** Other radiologic studies, such as intravenous pyelography and CT scans, are not indicated for routine follow-up of patients who do not have symptoms.

Serum CA125 measurement has been suggested for posttreatment surveillance of endometrial cancer (305,306,307). Elevated CA125 levels have been documented in patients with recurrent tumor, and these levels have correlated with the clinical course of disease. However, CA125 levels may be normal in the presence of small recurrences, making the utility of CA125 measurements for follow-up of patients after treatment of early-stage disease suspect. Determinations of CA125 should be obtained in patients with elevated levels at the time of diagnosis or with known extrauterine disease.

Estrogen Therapy after Treatment of Endometrial Cancer

A history of endometrial cancer has long been considered a contraindication to estrogen therapy because of the concern that occult metastatic disease might be activated by estrogen. Although this is a reasonable concern, the magnitude of this risk has never been quantified

and, in fact, **there is no evidence that estrogen therapy after apparently**

successful treatment of endometrial cancer increases the risk for cancer recurrence.

In a nonrandomized, retrospective follow-up study of 221 patients with clinical stage I endometrial cancer, 47 patients who had received estrogen after treatment were compared with 174 who had not been treated with estrogen. There were no significant differences between the two groups with respect to known risk factors for cancer recurrence. There were 26 (14.9%) recurrences in the patients not treated with estrogen, compared with only 1 (2.1%) recurrence in the patients treated with estrogen. Moreover, in the group not receiving estrogen, there were 26 deaths (16 from cancer and 10 from intercurrent disease), compared with only 1 death among those taking estrogen (308). Similarly in another report, no recurrent cancers and no intercurrent deaths were found in 44 women who took estrogen after treatment for endometrial cancer, compared with eight recurrences and eight intercurrent deaths (five from myocardial infarction) in 99 women who did not take estrogen (309). In a subsequent study of 123 surgical stage I and II endometrial cancer patients, 62 (50.5%) who received estrogen therapy postoperatively were identified. After controlling for risk factors for recurrence, there was no detectable difference in recurrence rate or time to recurrence between those patients who had received estrogen therapy and those who had not (310). More recently, a retrospective cohort study of matched treatment-control pairs found two recurrences (1%) among the 75 women using estrogen, compared with 11 recurrences (14%) in the 75 women not using estrogen after primary therapy for endometrial cancer (311). In all of these studies, however, most patients did not commence estrogen therapy immediately after surgery.

Many women who have been successfully treated for endometrial cancer suffer side effects of estrogen deficiency, such as vasomotor instability, vaginal dryness, and dyspareunia, as well as the long-term risk of osteoporosis. Because of the risk of hormone therapy for all women, its use in women previously treated for endometrial cancer should be considered carefully after the patient has been counseled about risks, benefits, and options. A compromise between immediate postoperative estrogen therapy and no hormone therapy might be to withhold estrogen for 1 to 3 years after treatment, the time in which most recurrences develop, thereby minimizing the chances of administering estrogen to patients with residual cancer. **Alternatively, topical estrogen alone can be used judiciously to treat vaginal symptoms. Symptomatic relief of hot flashes can be achieved by prescribing progestins such a *medroxyprogesterone acetate*, 10 mg orally daily or 150 mg intramuscularly every 3 months, or nonhormonal agents such as *Bellergal*, *clonidine*, and *venlafaxine*.**

Uterine Sarcoma

Uterine sarcomas are relatively rare tumors of mesodermal origin. They constitute 2% to 6% of uterine malignancies (312,313,314). There is an increased incidence of uterine sarcomas after radiation therapy to the pelvis for either carcinoma of the cervix or a benign condition. The relative risk of uterine sarcoma after pelvic radiotherapy has been estimated to be 5.38, with an interval of usually 10 to 20 years (315). Uterine sarcomas are, in general, the most malignant group of uterine tumors and differ from endometrial cancers with regard to diagnosis, clinical behavior, pattern of spread, and management.

Classification

The three most common histologic variants of uterine sarcoma are endometrial stromal sarcoma (ESS), leiomyosarcoma, and malignant mixed müllerian tumor (MMMT) of both homologous and heterologous type (316) (Table 33.18). Variations in the relative incidences of uterine sarcomas occur in different published series, probably

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related to the strictness of criteria used to classify smooth muscle and endometrial stromal tumors as sarcomas. In general, leiomyosarcoma and MMMT each make up about 40% of tumors, followed by ESS (15%) and other sarcomas (5%), although MMMT predominates in more recent reports. Staging of uterine sarcomas is based on the FIGO system for endometrial carcinoma (see Table 33.6 and 33.7).

Table 33.18 Classifications of Uterine Sarcomas

I. Pure nonepithelial tumors

A. Homologous

1. Endometrial stromal tumors

a. Low-grade stromal sarcoma

b. High-grade or undifferentiated stromal sarcoma

2. Smooth muscle tumors

a. Leiomyosarcoma

b. Leiomyoma variants

1. Cellular leiomyoma

2. Leiomyoblastoma (epithelioid leiomyoma)

c. Benign metastasizing tumors

1. Intravenous leiomyomatosis

2. Benign metastasizing leiomyoma

3. Disseminated peritoneal leiomyomatosis

B. Heterologous

1. Rhabdomyosarcoma

2. Chondrosarcoma

3. Osteosarcoma

4. Liposarcoma

II. Mixed epithelial–nonepithelial tumors**A. Malignant mixed mullerian tumor**

1. Homologous (carcinosarcoma)

2. Heterologous

B. Adenosarcoma

Modified from **Clement P, Scully RE**. Pathology of uterine sarcomas. In: **Coppleson M, ed**. *Gynecologic oncology: principles and practice*. New York, NY: Churchill-Livingston, 1981, with permission.

Endometrial Stromal Tumors

Stromal tumors occur primarily in perimenopausal women between ages 45 and 50 years; about one third occur in postmenopausal women. There is no relationship to parity, associated diseases, or prior pelvic radiotherapy. These tumors are rare in African-American women. The most frequent symptom is abnormal uterine bleeding; abdominal pain and pressure caused by an enlarging pelvic mass occur less often, and some patients do not have symptoms. Pelvic examination usually reveals regular or irregular uterine enlargement, sometimes associated with rubbery parametrial induration. The diagnosis may be determined by endometrial biopsy, but the usual preoperative diagnosis is uterine leiomyoma. At surgery, the diagnosis is suggested by the presence of an enlarged uterus filled with soft, gray-white to yellow necrotic and hemorrhagic tumors with bulging surfaces associated with wormlike elastic extensions into the pelvic veins.

Endometrial stromal tumors are composed purely of cells resembling normal endometrial stroma. They are divided into three types on the basis of mitotic activity, vascular invasion, and observed differences in prognosis: (i) endometrial stromal nodule, (ii) endometrial stromal sarcoma, and (iii) high-grade or undifferentiated sarcoma.

Endometrial stromal nodule is an expansive, noninfiltrating, solitary lesion confined to the uterus with pushing margins, no lymphatic or vascular invasion, and usually less than 5 mitotic figures per 10 high-power microscopic fields (5 MF/10 HPF). These tumors should be considered benign because there have been no recurrences or tumor-associated deaths reported after surgery (317,318).

Endometrial stromal sarcoma (formerly termed low-grade ESS or endolymphatic stromal myosis) is distinguished from high-grade ESS or undifferentiated endometrial sarcoma microscopically by a mitotic rate of less than 10 MF/10 HPF as well as clinically by a more protracted course. Recurrences typically occur late, and local recurrence is more common than distant metastases (319,320,321,322,323). Although endometrial stromal sarcoma often behaves in a histologically aggressive fashion, it lacks the aneuploid DNA content and high proliferative index associated with high-grade stromal sarcoma. Flow cytometric analysis can be used to differentiate the two conditions and predict response to therapy.

Endometrial stromal sarcoma has extended beyond the uterus in 40% of cases at the time of diagnosis, but the extrauterine spread is confined to the pelvis in two thirds of the cases. Upper-abdominal, pulmonary, and lymph node metastases are uncommon. Recurrence occurs in almost one half of cases at an average interval of about 5 years after initial therapy. Prolonged survival and even cure are not uncommon even after the development of recurrent or metastatic disease.

Optimum initial therapy for patients with endometrial stromal sarcoma consists of surgical excision of all grossly detectable tumor. Total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed. The adnexa should always be removed because of the propensity for tumor extension into the parametria, broad ligaments, and adnexal structures as well as the possible stimulating effect of estrogen from retained ovaries on the tumor cells. A beneficial effect of radiation therapy has been reported, and pelvic irradiation is recommended for inadequately excised or locally recurrent pelvic disease (319). There is also evidence that endometrial stromal sarcoma is hormone dependent or responsive.

(323). Recurrent or metastatic lesions may also be amenable to surgical excision. Long-term survival and apparent cures have been noted in patients with pulmonary metastases (324).

High-grade ESS or undifferentiated endometrial sarcoma is a highly malignant neoplasm. Histologically, it exhibits greater than 10 MF/10 HPF and often completely lacks recognizable stromal differentiation. This tumor has a much more aggressive clinical course and poorer prognosis than endometrial stromal sarcoma (316,319,325,326,327). The 5-year disease-free survival is about 25%. Treatment of undifferentiated endometrial sarcoma should consist of total abdominal hysterectomy and bilateral salpingo-oophorectomy. The poor therapeutic results obtained to date suggest that radiation therapy, chemotherapy, or both should be used in combination with surgery. These tumors, unlike endometrial stromal sarcoma, are not responsive to progestin therapy.

Uterine tumor resembling ovarian sex-cord tumor (UTROSCT) is a rare variant of endometrial stromal sarcoma in which benign glands and epithelial cells are found. Immunohistochemically, these tumors express cytokeratin, epithelial membrane antigen, vimentin, and smooth muscle actin. Although some of these tumors have infiltrative margins, almost all of them behave benignly. The so-called mixed UTROSCT have a significant endometrial stromal sarcoma component and tend to behave more aggressively (328,329).

Leiomyosarcoma

The median age for women with leiomyosarcoma (43 to 53 years) is somewhat lower than that for other uterine sarcomas, and premenopausal patients have a better chance of survival. This malignancy has no relationship with parity, and the incidence of associated diseases is not as high as in MMMT or endometrial adenocarcinoma. African-American women have a higher incidence and a poorer prognosis than women of other races. A history of prior pelvic radiation therapy can be elicited in about 4% of patients with leiomyosarcoma. The incidence of sarcomatous change in benign uterine leiomyomas is reported to be between 0.13% and 0.81% (330,331,332,333,334,335,336,337,338,339,340).

Presenting symptoms, which usually are of short duration (mean, 6 months) and not specific to the disease, include vaginal bleeding, pelvic pain or pressure, and awareness of an abdominopelvic mass. The principal physical finding is the presence of

a pelvic mass. The diagnosis should be suspected if severe pelvic pain accompanies a pelvic tumor, especially in a postmenopausal woman. Endometrial biopsy, although not as useful as in other sarcomas, may establish the diagnosis in as many as one third of cases when the lesion is submucosal.

Survival rates for patients with uterine leiomyosarcoma range from 20% to 63% (mean, 47%). The pattern of tumor spread is to the myometrium, pelvic blood vessels and lymphatics, contiguous pelvic structures, abdomen, and then distantly, most often to the lungs. The number of mitoses in the tumor has traditionally been the most reliable microscopic indicator of malignant behavior (see Fig. 33.8).

Generally, tumors with less than 5 MF/10 HPF behave in a benign fashion, and tumors with more than 10 MF/10 HPF are frankly malignant with a poor prognosis. Tumors with 5 to 10 MF/10 HPF, termed *cellular leiomyomas* or *smooth muscle tumors of uncertain malignant potential*, are less predictable. Therefore, in addition to mitotic index greater than 10, other histologic indicators used to classify uterine smooth muscle tumors as malignant are severe cytologic atypia and coagulative tumor cell necrosis (341). Uterine smooth muscle tumors with any two of these three features are associated with a poor prognosis. Gross presentation of the tumor at the time of surgery is also an important prognostic indicator. Tumors with infiltrating tumor margins or extension beyond the uterus are associated with poor prognosis, whereas tumors less than 5 cm, originating within myomas, or with pushing margins are associated with prolonged survival.

Five other clinical pathologic variants of uterine smooth muscle tumors deserve special comment: (i) myxoid leiomyosarcoma, (ii) leiomyoblastoma, (iii) intravenous leiomyomatosis, (iv) benign metastasizing uterine leiomyoma, and (v) disseminated peritoneal leiomyomatosis.

***Myxoid leiomyosarcoma* is characterized grossly by a gelatinous appearance and apparent circumscribed border.** Microscopically, the tumors have a myxomatous stroma and extensively invade adjacent tissue and blood vessels (342). The mitotic rate is low (0-2 MF/10 HPF), which belies their aggressive behavior and poor prognosis. Surgical excision by hysterectomy is the mainstay of treatment. The low mitotic rate and abundance of intracellular myxomatous tissue suggest that these tumors would not be responsive to radiation therapy or chemotherapy.

***Leiomyoblastoma* includes smooth muscle tumors designated as epithelioid leiomyomas, clear cell leiomyomas, and plexiform tumorlets (343,344).** This group of

atypical smooth muscle tumors is distinguished by the predominance of rounded rather than spindle-shaped cells and by a clustered or cordlike pattern. These lesions should be regarded as specialized low-grade leiomyosarcomas with fewer than 5 MF/10 HPF. Leiomyoblastoma is treated with hysterectomy, and the prognosis is excellent.

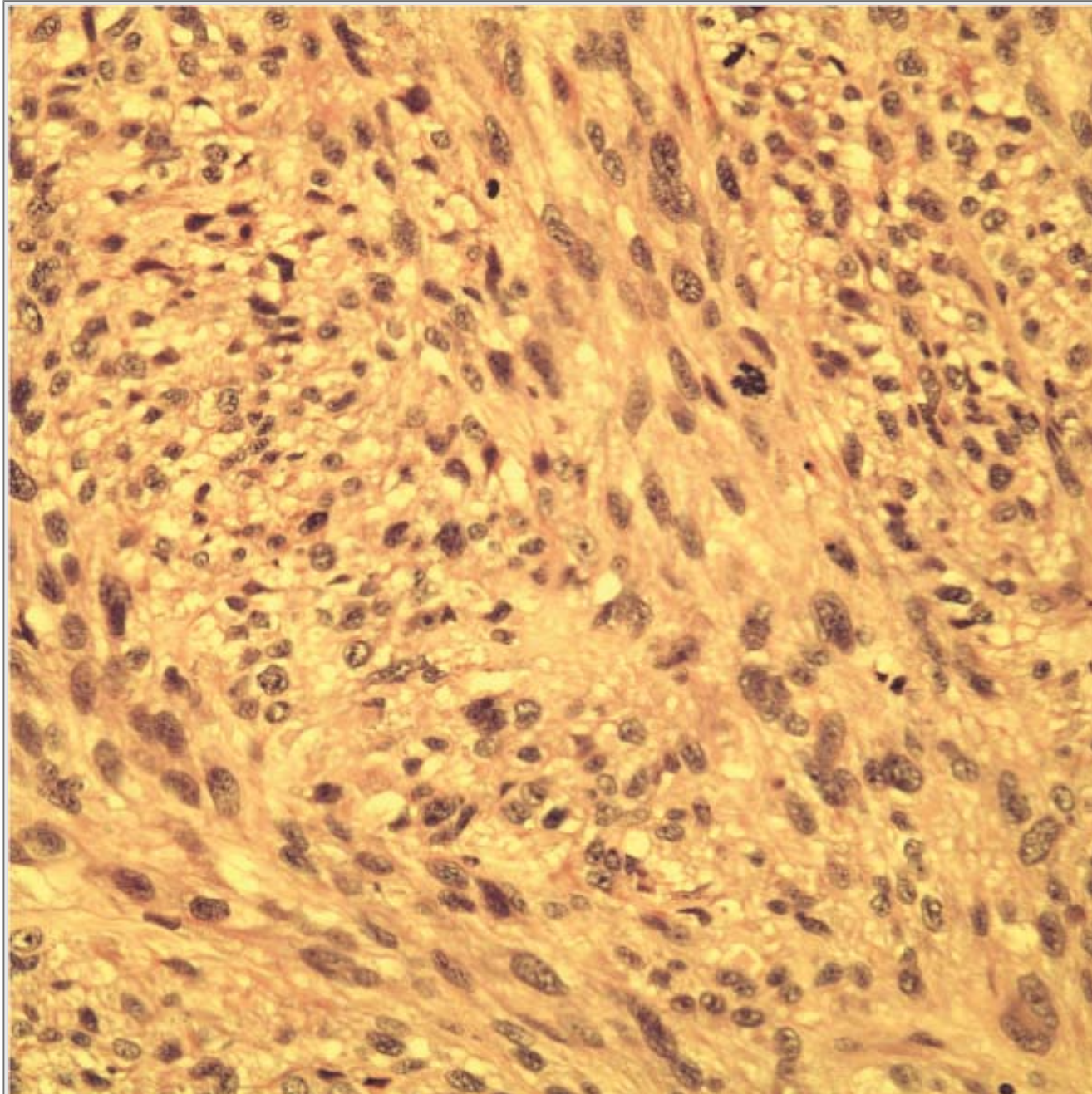


Figure 33.8 Leiomyosarcoma of the uterus. Interlacing bundles of spindle cells have fibrillar cytoplasm, irregular and hyperchromatic nuclei, and multiple mitotic figures. (Provided by Gordana Stevanovic, MD, and Jianyu Rao, MD, Department of Pathology, UCLA.)

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Intravenous leiomyomatosis is characterized by the growth of histologically benign smooth muscle into venous channels within the broad ligament and then into uterine and iliac veins (345,346,347,348). The intravascular growth takes the form of visible, wormlike projections that extend out from a myomatous uterus into the parametria toward the pelvic sidewalls. It may be confused with low-grade stromal sarcoma. Symptoms are related to the associated uterine myomas. Most patients are in the late fifth and early sixth decades of life. The prognosis is excellent, even when tumor is left in pelvic vessels. Late local recurrences can occur, and deaths from extension into the inferior vena cava or metastases to the heart have been reported. Estrogen may stimulate the proliferation of these intravascular tumors. Treatment should be total abdominal hysterectomy and bilateral salpingo-oophorectomy with removal of as much of the tumor as possible.

Benign metastasizing uterine leiomyoma is a rare condition in which a histologically benign uterine smooth muscle tumor acts in a somewhat malignant fashion and produces benign metastases, usually to the lungs or lymph nodes (349). In most instances, intravenous leiomyomatosis is not apparent. The metastasizing myomas are capable of growth at distant sites, whereas the intravenous tumors spread only by direct extension within blood vessels. Both experimental and clinical evidence suggests that

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these tumors are stimulated by estrogen. Therefore, removing the source of estrogen, by castration or withdrawal of exogenous estrogen, or by treatment with progestins, *tamoxifen*, or a gonadotropin agonist, has an ameliorating effect (350). Surgical treatment should consist of total abdominal hysterectomy and bilateral salpingo-oophorectomy as well as resection of pulmonary metastases, if possible.

Disseminated peritoneal leiomyomatosis is a rare clinical entity characterized by benign smooth muscle nodules scattered throughout the peritoneal cavity (351). This condition probably arises as a result of metaplasia of subperitoneal mesenchymal stem cells to smooth muscle, fibroblasts, myofibroblasts, and decidual cells under the influence of estrogen

and progesterone. Most reported cases have occurred in 30- to 40-year-old women who are or who have recently been pregnant or who have a long history of oral contraceptive use. Intriguing features of this disease are its grossly malignant appearance, benign histology, and favorable clinical outcome. Intraoperative diagnosis requires frozen-section examination. Extirpative surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and excision of as much gross disease as possible may be indicated in menopausal women. Removal of the source of excess estrogen, treatment with progestins, or both has resulted in regression of unresected tumor masses. Almost all patients have a good prognosis.

Malignant Mixed Müllerian Tumors

Malignant mixed müllerian tumors are composed histologically of a mixture of sarcoma and carcinoma. The carcinomatous element is usually glandular, whereas the sarcomatous element may resemble the normal endometrial stroma (homologous or the so-called carcinosarcoma), or it may be composed of tissues foreign to the uterus, such as cartilage, bone, or striated muscle (heterologous). These tumors are most likely derived from totipotential endometrial stromal cells (352,353,354,355).

Almost all of these tumors occur after menopause, at a median age of 62 years.

The incidence is higher in African-American women. These tumors are often found in association with other medical conditions, such as obesity, diabetes mellitus, and hypertension. A history of previous pelvic irradiation can be obtained in 7% to 37% of patients.

The most frequent presenting symptom is postmenopausal bleeding, which occurs in 80% to 90% of cases. Other less common symptoms are vaginal discharge, abdominal or pelvic pain, weight loss, and passage of tissue from the vagina. The duration of symptoms usually is only a few months. On physical examination, uterine enlargement is present in 50% to 95% of patients, and a polypoid mass may be seen within or protruding from the endocervical canal in up to 50% of patients. Diagnosis can usually be determined by biopsy of an endocervical mass or endometrial curettage.

The tumor grows as a large, soft, polypoid mass filling and distending the uterine cavity; necrosis and hemorrhage are prominent features. The myometrium is invaded to various degrees in almost all cases. The most frequent areas of spread are the pelvis, lymph nodes, peritoneal cavity, lungs, and liver. This metastatic pattern suggests that these neoplasms spread by local extension and regional lymph node metastasis in a manner similar to that of

endometrial adenocarcinoma, although they behave more aggressively.

The most important single factor affecting prognosis in patients with MMMT is the extent of tumor at the time of treatment. One study noted that in patients with tumor apparently confined to the uterine corpus (stage I), the 2-year survival rate was 53%, whereas the survival rate dropped to 8.5% when disease had extended to the cervix, vagina, or parametria (stage II and III); no patients with disease outside the pelvis (stage IV) survived (356). In another study, 5-year survival for patients with disease confined to the corpus (74%) was significantly greater than for those with more advanced disease (24%) (357).

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Unfortunately, disease has extended outside the uterus in 40% to 60% of cases at the time of diagnosis, indicating the highly malignant nature of this lesion. Even when disease is believed to be confined to the uterus preoperatively and potentially is still curable, surgical and pathologic staging identifies extrauterine spread of disease in a significant number of cases. In one study, 55% of women with clinical stage I MMMT had a higher surgical—pathologic stage. Only 28% of tumors were actually confined to the uterine corpus, 16% had extension to the cervix, and 56% showed extrauterine spread (358). In a significant number of patients, lymph node metastases and positive peritoneal cytology has been found with early-stage MMMT (357,359,360). Deep myometrial invasion, which is present in about one half of stage I cases, is associated with poor prognosis. Almost all patients in whom tumor involves the outer one half of the myometrium die from the disease. Patients who die from MMMT tend to have larger tumors and a higher incidence of LVSI. Patients with a history of prior pelvic irradiation generally have a poorer prognosis. Overall, the 5-year survival rate for patients with MMMT is about 20% to 30%.

Adenosarcoma is an uncommon variant of MMMT (361,362). It consists of an admixture of benign-appearing neoplastic glands and a sarcomatous stroma. Most patients present with postmenopausal vaginal bleeding, and the disease is diagnosed or suspected based on endometrial curettage. Most adenosarcomas are well circumscribed and limited to the endometrium or superficial myometrium. The treatment is hysterectomy and bilateral salpingo-oophorectomy, with or without adjuvant radiotherapy. Because recurrences, mostly in the form of local pelvic or vaginal disease, have been reported in 40% to 50% of cases, adjuvant postoperative intravaginal or pelvic irradiation has been recommended.

Treatment

Recurrences develop in more than one half of cases of uterine sarcoma, even when disease is apparently localized at the time of treatment (363,364,365). At least one half of recurrences occur outside the pelvis, with isolated pelvic failures accounting for less than 10% of recurrences. The most common sites of recurrence are the abdomen and lungs. These data emphasize that the major limitation to cure of uterine sarcomas is distant spread.

Based on this type of evidence, treatment of most stage I and II uterine sarcomas should include hysterectomy, bilateral salpingo-oophorectomy, and treatment of the pelvic lymphatics by irradiation or surgery. Strong consideration should also be given to the use of adjuvant chemotherapy to decrease the incidence of distant metastases. Stage III uterine sarcomas are probably best treated by an aggressive combined approach of surgery, radiation therapy, and chemotherapy. Stage IV disease must be treated with combination chemotherapy.

Surgery

The first step in the treatment of early uterine sarcoma should be exploratory laparotomy. Because extirpative survey is the most important aspect of treatment, and knowledge of the extent and spread of the disease is important for further management, one should not forego or delay surgery by using radiation therapy or chemotherapy first. At the time of surgery, the peritoneal cavity should be carefully explored and peritoneal washings obtained. Special attention should be given to the pelvic and para-aortic lymph nodes; selected lymphadenectomies should be performed with ESS and MMT, but are not necessary in leiomyosarcoma, in which the risk of lymph node metastases is low. **Total abdominal hysterectomy is the standard procedure, and bilateral salpingo-oophorectomy should also be performed in all patients except premenopausal women with leiomyosarcoma.** Based on the surgical and pathologic findings, additional therapy with radiation therapy or chemotherapy can then be planned. Rarely, a patient may be cured by excision of an isolated pulmonary metastasis (366,367).

Radiation Therapy

Most studies have found adjuvant preoperative or postoperative radiation therapy to be of value in decreasing pelvic recurrences and thereby increasing quality of life in

patients with localized ESS and MMMT, but not with leiomyosarcoma (368,369,370,371,372,373,374,375,376). Radiation therapy thus appears to have a role used in combination with surgery in the treatment of MMMT and ESS confined to the pelvis. By increasing the disease-free progression interval and pelvic control, radiation therapy probably increases the overall survival to some degree.

Chemotherapy

Several chemotherapeutic agents have been found to have activity in sarcomas, including *vincristine*, *actinomycin D*, *cyclophosphamide*, *doxorubicin*, *dimethyl triazeno imidazole carboxamide (dacarbazine, DTIC)*, *cisplatin*, *ifosfamide* *paclitaxel*, *gemcitabine*, and *liposomal doxorubicin* (377). *Doxorubicin* appears to be the most active single agent in the treatment of leiomyosarcoma, producing a 25% response rate (378). *Ifosfamide* also has some activity to a lesser degree (379). On the other hand, *cisplatin* and *ifosfamide* have demonstrated clear activity in MMMT, with responses rates of 18% to 42% and 32%, respectively (380,381,382). *Doxorubicin* has demonstrated less than a 10% response rate in MMMT (378). *Paclitaxel* yielded an 18% response rate with MMMT (383), but had limited activity in leiomyosarcomas (384). *Gemcitabine* (385) and *liposomal doxorubicin* (386) have shown activity in leiomyosarcomas.

Combination chemotherapy with *doxorubicin* and *DTIC*, or these two drugs plus *vincristine* and *cyclophosphamide*, has been reported to yield somewhat higher response rates (387,388,389). Similarly, *ifosfamide* has been combined with *mesna uroprotection*, *doxorubicin*, and *DTIC* to treat metastatic pure sarcomas (390). More recently, *gemcitabine* has been combined with *docetaxel* for treatment of metastatic leiomyosarcoma, yielding an overall response rate of 53%, including patients previously treated with *doxorubicin* (391). Combined *ifosfamide* and *cisplatin* chemotherapy has resulted in a higher response rate (54% versus 36%) and a longer progression-free survival than *ifosfamide* chemotherapy alone for treatment of advanced MMMT (392). **A combination of *paclitaxel* and *carboplatin* for treatment of advanced uterine MMMT was recently reported to result in a complete response rate of 80% (four fifths) and a median progression-free interval of 18 months** (393).

Adjuvant Treatment

Because of the relatively low survival rate in localized uterine sarcomas and the high incidence

of failure resulting from subsequent distant metastasis, adjuvant treatment programs employing chemotherapy have been tested (394,395,396,397). Unfortunately, **most reports have been unable to show a clear improvement in survival by the addition of postoperative adjuvant chemotherapy in early uterine sarcoma**. The GOG conducted a trial of postoperative adjuvant *doxorubicin* in stage I and II uterine sarcoma patients. Of the 75 patients randomized to receive *doxorubicin*, 41% developed a recurrence, compared with 53% of 81 patients receiving no adjuvant chemotherapy, but these differences were not significant (394). Other smaller, nonrandomized adjuvant chemotherapy studies employing *cyclophosphamide*, *cisplatin* plus *doxorubicin*, and *ifosfamide* plus *cisplatin* reported recurrence rates of 33%, 24%, and 31%, respectively (395,396,397).

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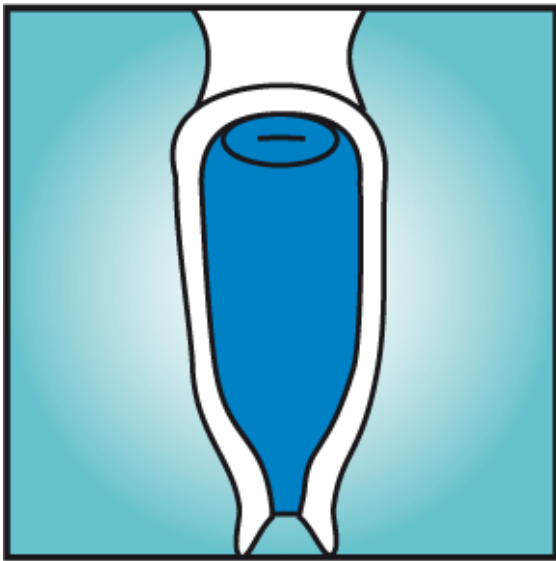
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34

Cervical and Vaginal Cancer

Michael A. Bidus

John C. Elkas



- **Human papillomavirus (HPV) infection is the causal agent of cervical cancer.**
- **Screening programs are effective at decreasing the incidence of cervical cancer.**
- **Although the most common histologic type of cervical cancer is squamous, the relative and absolute incidence of adenocarcinoma is increasing.**
- **Cervical cancer is clinically staged, although modern radiographic modalities such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, or positron emission tomography (PET) may be beneficial for individual treatment planning.**
- **Treatment of cervical cancer is based on stage of disease. In general, early stage disease (I–IIa) can be treated with either radical surgery or radiation therapy. Advanced stage disease (IIb–IV) is best treated with chemoradiation.**
-

Vaginal cancer is a rare disease with many similarities to cervical cancer. Radiation therapy is the mainstay of treatment for most patients; however, select patients may be treated with radical surgery.

Cervical cancer ranks as the third most common gynecologic neoplasm in the United States, behind cancer of the corpus and ovary, mainly as a result of the effectiveness of screening programs. **Worldwide, cervical carcinoma continues to be a significant health care problem. In third world countries, where limited health care resources exist, cervical carcinoma remains a significant cause of mortality.** Because cervical cancer is preventable, it is imperative that gynecologists and other primary care providers who administer health care to women be familiar with screening techniques, diagnostic procedures, and risk factors for cervical cancer as well as management of preinvasive disease. Vaginal cancer is a rare tumor that shares a similar epidemiology and risk factor profile as cervical cancer.

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Cervical Cancer

Epidemiology and Risk Factors

Invasive cancer of the cervix is considered a preventable disease because it has a long preinvasive state, cervical cytology screening programs are currently available, and the treatment of preinvasive lesions is effective. In spite of the preventable nature of this disease, however, 9710 new cases of invasive cervical cancer resulting in 3700 deaths were anticipated in the United States in 2006 (1). Nationally, the lifetime probability of developing cervical cancer is 1:128. Although screening programs in the United States are well established, it is estimated that 30% of cervical cancer cases will occur in women who have never had a Pap test. In developing countries, this percentage approaches 60% (2). In spite of these statistics, the worldwide incidence of invasive disease is decreasing, and cervical cancer is being diagnosed earlier, leading to better survival rates (1,3). The mean age for cervical cancer in the United States is 47 years, and the distribution of cases is bimodal, with peaks at 35 to 39 years and 60 to 64 years of age (1).

There are numerous risk factors for cervical cancer: young age at first intercourse (<16 years), multiple sexual partners, cigarette smoking, race, high parity, and lower socioeconomic status. The relationship to oral contraceptive use has been debated. Some investigators have proposed that use of oral contraceptives may increase the incidence of cervical glandular abnormalities (4,5); however, this hypothesis has not been consistently supported. Many of these risk factors are linked to sexual activity and exposure to sexually transmitted diseases. Infection with the herpes virus was previously thought to be the initiating event in cervical cancer; however, infection with human papillomavirus (HPV) has now been determined to be the causal agent in the development of cervical cancer, with herpes virus and *Chlamydia trachomatis* likely acting as cofactors. The role of human immunodeficiency virus (HIV) in cervical cancer is thought to be mediated through immune suppression. The Centers for Disease Control and Prevention have described cervical cancer as an acquired immune deficiency syndrome (AIDS)—defining illness in patients infected with HIV (6).

The initiating event in cervical dysplasia and carcinogenesis is infection with HPV. HPV infection has been detected in up to 99% of women with squamous cervical carcinoma (7). There are more than 100 different types of HPV, and more than 30 of which can affect the lower genital tract. There are 14 high-risk HPV subtypes; two of the high-risk subtypes, 16 and

18, are found in up to 62% of cervical carcinomas. The mechanism by which HPV affects cellular growth and differentiation is through the interaction of viral E6 and E7 proteins with tumor suppressor genes p53 and Rb, respectively. Inhibition of p53 prevents cell cycle arrest and cellular apoptosis, which normally occurs when damaged DNA is present, whereas inhibition of Rb disrupts transcription factor E2F, resulting in unregulated cellular proliferation (8). Both steps are essential for the malignant transformation of cervical epithelial cells.

Evaluation

Vaginal bleeding is the most common symptom occurring in patients with cancer of the cervix. Most often, this is postcoital bleeding, but it may occur as irregular or postmenopausal bleeding as well. Patients with advanced disease may present with a malodorous vaginal discharge, weight loss, or obstructive uropathy. In asymptomatic women, cervical cancer is most commonly identified through evaluation of abnormal cytologic screening tests.

Initially, all women suspected of having cervical cancer should have a general physical examination performed to include evaluation of the supraclavicular, axillary, and inguinofemoral lymph nodes to exclude the presence of metastatic disease. On pelvic

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examination, a speculum is inserted into the vagina, and the cervix is inspected for suspicious areas (Fig. 34.1). The vaginal fornices should also be closely inspected. With invasive cancer, the cervix is usually firm and expanded, and these features should be confirmed by digital examination. Rectal examination is also important to help establish cervical consistency and size, particularly in patients with endocervical carcinomas. Additionally, rectal examination is the only way to determine cervical size if the vaginal fornices have been obliterated by menopausal changes or by the extension of disease. Parametrial extension of disease is best determined by the finding of nodularity beyond the cervix on rectal examination.

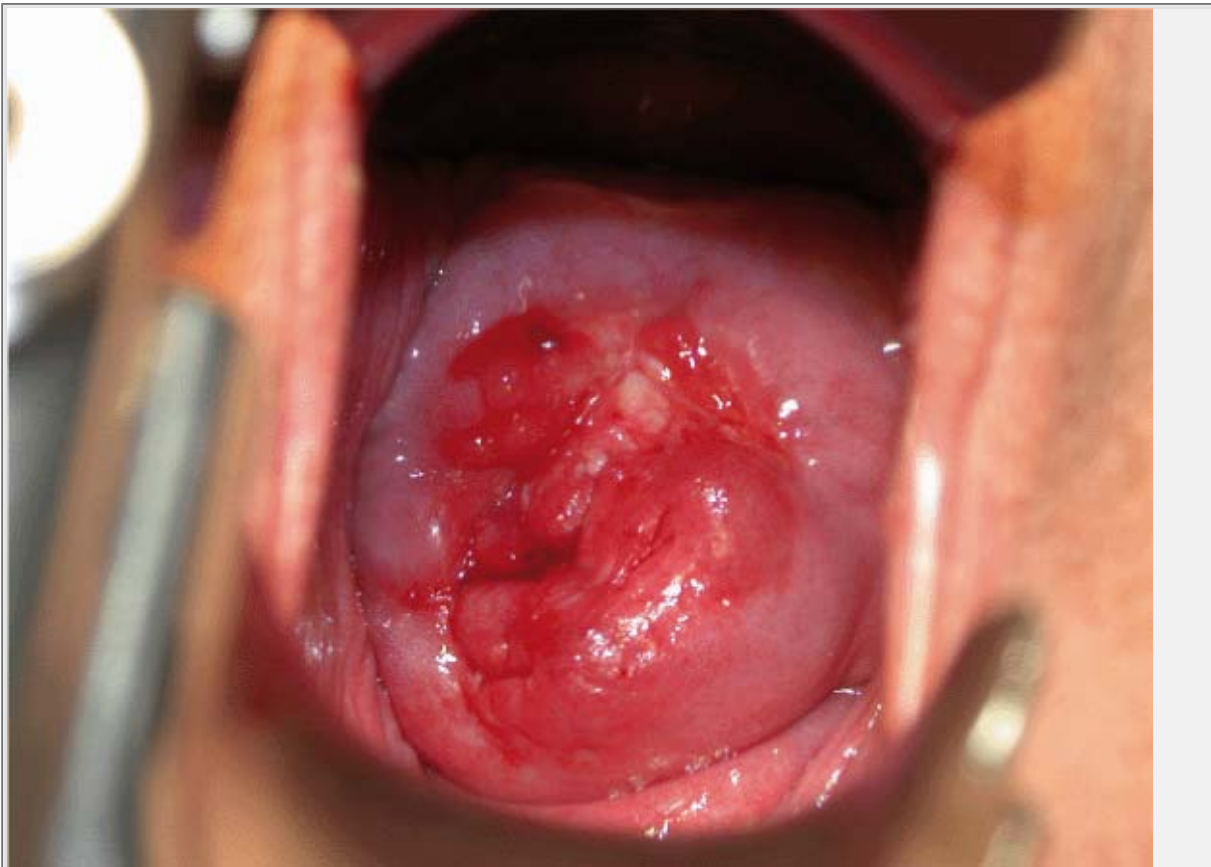


Figure 34.1 Gross appearance of cervical cancer on examination.

When obvious tumor growth is present, a cervical biopsy is usually sufficient for diagnosis. If gross disease is not present, a colposcopic examination with cervical biopsies and endocervical curettage is warranted. If the diagnosis cannot be established conclusively with colposcopy and directed biopsies, cervical conization may be necessary.

Colposcopic Findings of Invasion

Colposcopic examination is mandatory for patients with suspected early invasive cancer based on cervical cytology and a grossly normal-appearing cervix. Colposcopic findings that suggest invasion are (i) abnormal blood vessels, (ii) irregular surface contour with loss of surface epithelium, and (iii) color tone change. Colposcopically directed biopsies may permit the diagnosis of frank invasion and thus avoid the need for diagnostic cone biopsy, allowing treatment to be administered without delay. If there is debate about the depth of invasion based on the cervical biopsies, and if the clinical stage may be upstaged to stage Ia2 or Ib1, the patient should undergo a conization. In the presence of a large cervical biopsy specimen showing invasion greater than 3 mm or two biopsy specimens separated by 7 mm showing invasive cervical carcinoma, therapy should proceed without delay, and the patient could undergo radical surgery or radiation therapy.

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Abnormal Blood Vessels

Abnormal vessels may be looped, branched, or reticular. **Abnormal looped vessels are the most common colposcopic finding and arise from the punctated and mosaic vessels present in cervical intraepithelial neoplasia (CIN).** As the neoplastic growth process proceeds and the need for oxygen and nutrition increases, angiogenesis occurs as a result of tumor and local tissue production of VEGF, PDGF, EGF, and other cytokines, resulting in the proliferation of blood vessels and neovascularization. Punctate vessels push out over the surface of the epithelium in an erratic fashion, producing the looped, corkscrew, or J-shaped pattern of abnormal vessels characteristic of invasive disease. Abnormal blood vessels also arise from the cervical stroma and are pushed to the surface as the underlying cancer invades. The normally branching cervical stromal vessels are best observed over nabothian cysts. In this area, the branches are generally at acute angles, with the caliber of vessels becoming smaller after branching, much like the arborization of a tree. The abnormal branching blood vessels seen with cancer tend to form obtuse or right angles, with the caliber sometimes enlarging after branching. Sharp turns, dilations, and luminal narrowing also characterize these vessels. The surface epithelium may be lost in these areas, leading to irregular surface contour and friability.

Abnormal reticular vessels represent the terminal capillaries of the cervical epithelium. Normal capillaries are best seen in postmenopausal women with atrophic epithelium. When cancer involves this epithelium, the surface is eroded, and the capillary network is exposed. These vessels are very fine and short, and appear as small comma-shaped vessels without an organized pattern. They are not specific to invasive cancer; atrophic cervicitis may also have this appearance.

Irregular Surface Contour

Abnormal surface patterns are observed as tumor growth proceeds. The surface epithelium ulcerates as the cells lose intercellular cohesiveness secondary to loss of desmosomes. Irregular contour also may occur as a result of papillary characteristics of the lesion. **This finding can be confused with a benign HPV papillary growth on the cervix. For that reason, biopsies should be performed on all papillary cervical growths to avoid missing invasive disease.**

Color Tone

Color tone may change as a result of increasing vascularity, surface epithelial necrosis, and in some cases, production of keratin. The color tone is yellow-orange rather than the expected pink of intact squamous epithelium or the red of the endocervical epithelium.

Adenocarcinoma

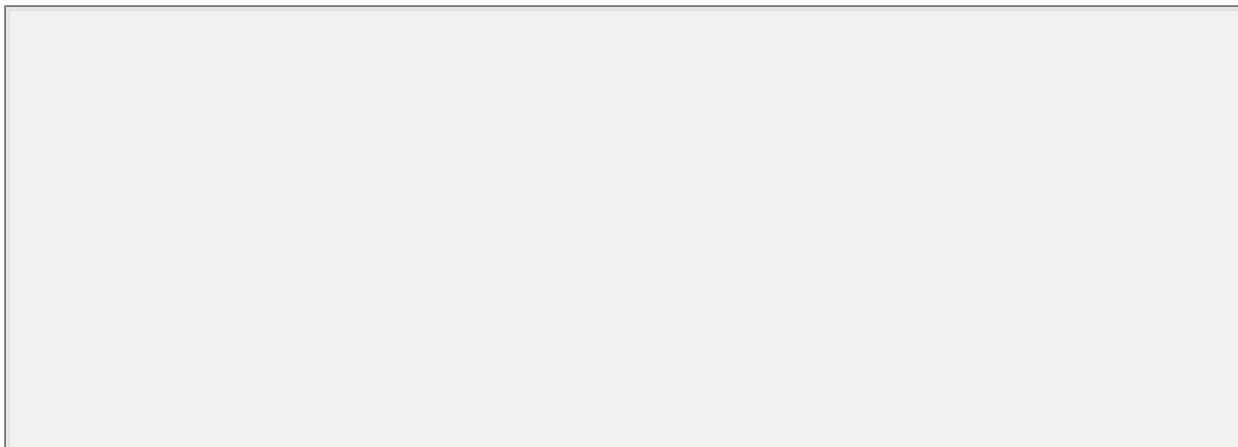
Adenocarcinoma of the cervix does not have a specific colposcopic appearance. All of the aforementioned blood vessels may be seen in these lesions as well. Because adenocarcinomas tend to develop within the endocervix, endocervical curettage is required as part of the colposcopic examination.

Histologic Appearance of Invasion

Cervical conization is required to assess correctly the depth and the linear extent of involvement when microinvasion is suspected. Early invasion is characterized by a protrusion of malignant cells from the stromal–epithelial junction. This focus consists of cells that appear better differentiated than the adjacent noninvasive cells and have abundant pink-staining cytoplasm, hyperchromatic nuclei, and small- to medium-sized nucleoli (9). **These early invasive lesions form tongue-like processes without measurable volume and are classified as International Federation of Gynecology and Obstetrics (FIGO) stage Ia1.** With further progression, more tongue-like processes and isolated malignant cells appear in the stroma, followed by a proliferation of fibroblasts (desmoplasia) and a bandlike infiltration of chronic inflammatory cells (Fig. 34.2). **With increasing depth of invasion, lesions occur at multiple sites, and the growth becomes measurable by depth and linear extent. Lesions that are smaller than 3 mm are classified as FIGO stage Ia1. Lesions that are 3 to 5 mm or more in depth and up to 7 mm in linear**

extent are classified as FIGO stage Ia2 (10). As the depth of stromal invasion increases, the risk of capillary lymphatic space involvement is increased. Dilated capillaries, lymphatic spaces, and foreign-body multinucleated giant cells containing keratin debris are often seen in the stroma.

P.1407



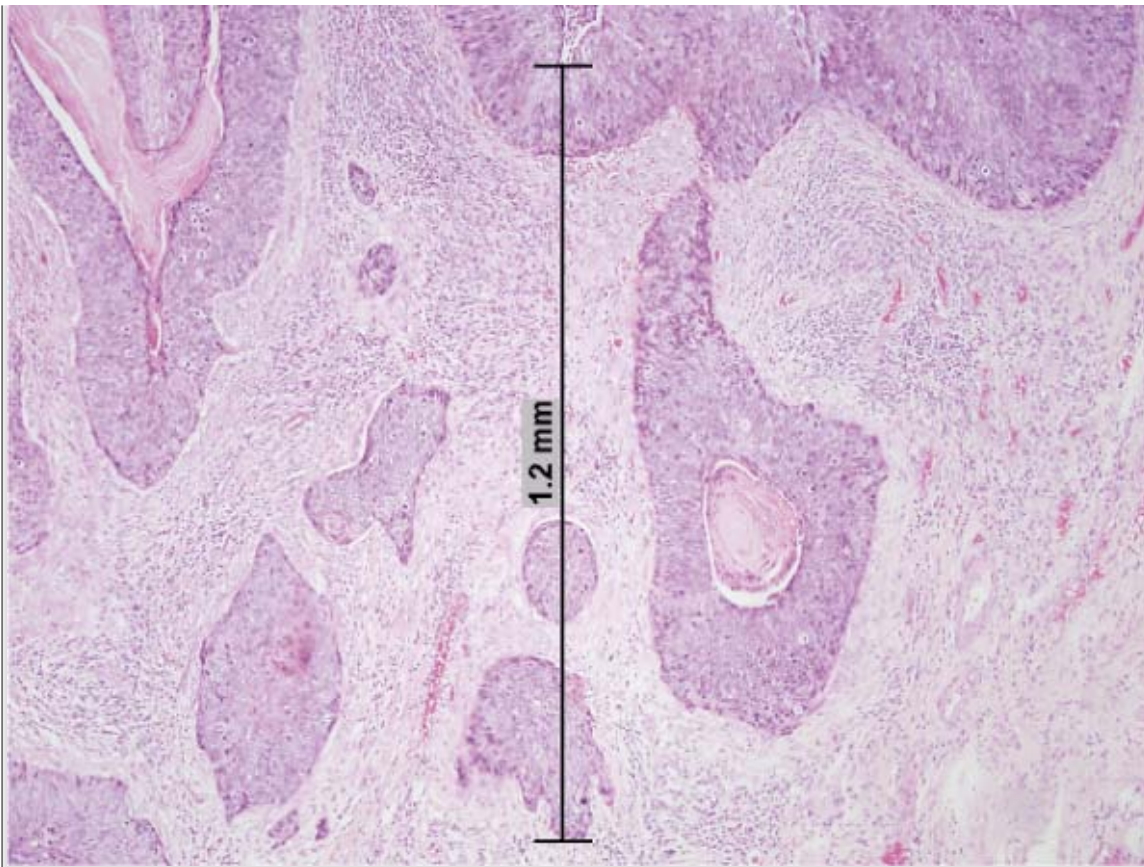


Figure 34.2 Microinvasive squamous carcinoma. Multiple irregular tongue-like processes and isolated nests of malignant cells are seen, some surrounded by clear spaces, simulating capillary lymphatic invasion. This is an artifact caused by tissue shrinkage. The depth of stromal invasion is measured from the basement membrane of the overlying cervical intraepithelial neoplasia (CIN). In this case, it is 1.2 mm.

The depth of invasion should be measured with a micrometer from the base of the epithelium to the deepest point of invasion. **Depth of invasion is a significant predictor for the development of pelvic lymph node metastasis and tumor recurrence. Although lesions that have invaded 3 mm or less rarely metastasize, patients in whom lesions invade between 3 to 5 mm have positive pelvic lymph nodes in 3% to 8% of cases (11).** Although the significance of the cutoff at 3 mm has not been identified completely, it has been postulated that small capillary—lymphatic spaces at this level are incapable of facilitating the transport of malignant cells. Uneven shrinkage of tissue by fixative often creates space between the tumor nests and the surrounding fibrous stroma, simulating vascular lymphatic invasion (see Fig. 34.2). Therefore, suspected vascular—lymphatic involvement with invasion of less than 3 mm should be interpreted with care. A lack of endothelial lining indicates that the space is a fixation artifact rather than true vascular invasion.

Staging

Cervical cancer is a clinically staged disease. The FIGO staging system is the current standard and is applicable to all histologic types of cervical cancer. The current FIGO staging system is presented in Table 34.1 and Figure 34.3. The staging procedures allowed by FIGO are listed in Table 34.2. **When there is doubt concerning the stage to which a**

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cancer should be allocated, the earlier stage should be selected. After a clinical stage

is assigned and treatment has been initiated, the stage must not be changed because of subsequent findings by either extended clinical staging or surgical staging.

The "upstaging" of patients during treatment will produce an erroneous perception of improvement in the results of treatment of low-stage disease. Following is a breakdown of the incidence of cervical cancer by stage at diagnosis: 38%, stage I; 32%, stage II; 26%, stage III; and 4%, stage IV (3,10,12).

Table 34.1 FIGO Staging of Carcinoma of the Cervix Uteri

Preinvasive Carcinoma	
Stage 0	Carcinoma <i>in situ</i> , intraepithelial carcinoma (cases of stage 0 should not be included in any therapeutic statistics).
Invasive Carcinoma	
Stage I^a	Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded).
	Stage Ia Preclinical carcinomas of the cervix, that is, those diagnosed only by microscopy.
	Stage Ia1 Lesion with ≤ 3 mm invasion.
	Ia2 Lesions detected microscopically that can be measured. The upper limit of the measurement should show a depth of invasion of >3 – 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates, and a second dimension, the horizontal spread, must not exceed 7 mm. Larger lesions should be staged as Ib.
	Ib Lesions invasive > 5 mm.
	Stage Ib1 Lesion ≤ 4 cm.
	Ib2 Lesions > 4 cm.
Stage II^b	The carcinoma extends beyond the cervix but has not extended onto the wall.
	The carcinoma involves the vagina, but not the lower one third.
	Stage IIa No obvious parametrial involvement.
	IIb Obvious parametrial involvement.
Stage III^c	The carcinoma has extended onto the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower one third of the vagina. All cases with hydronephrosis or nonfunctioning kidney.
	Stage IIIa No extension to the pelvic wall.
	IIIb Extension onto the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV^d	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.
	Stage IVa Spread to the growth to adjacent organs.
	IVb Spread to distant organs.

^a The diagnosis of both stages Ia1 and Ia2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion. The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7 mm. Vascular space involvement, either venous or lymphatic, should not alter the staging but should be specifically recorded because it may affect treatment decisions in the future. Lesions of greater size should be staged as Ib. As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

^b A patient with a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to stage IIb.

At clinical examination, it is impossible to decide whether a smooth, indurated parametrium is truly cancerous or only inflammatory. Therefore, the case should be assigned to stage III only if the parametrium is nodular to the pelvic wall or the growth itself extends to the pelvic wall.

^cThe presence of hydronephrosis or nonfunctioning kidney due to stenosis of the ureter by cancer permits a case to be allotted to stage III even if, according to other findings, it should be allotted to stage I or II.

^dThe presence of the bullous edema, as such, should not permit a case to be allotted to stage IV. Ridges and furrows into the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the growth at palpation (ie, examination from the vagina or the rectum during cystoscopy). A cytologic finding of malignant cells in washings from the urinary bladder requires further examination and a biopsy specimen from the wall of the bladder.

FIGO, International Federation of Gynecology and Obstetrics.

From **Benedet JL, Odicino F, Maisonneuve P, et al.** Carcinoma of the cervix uteri. *Int J Gynecol Obstet* 2003;83(suppl 1):27-39, with permission.

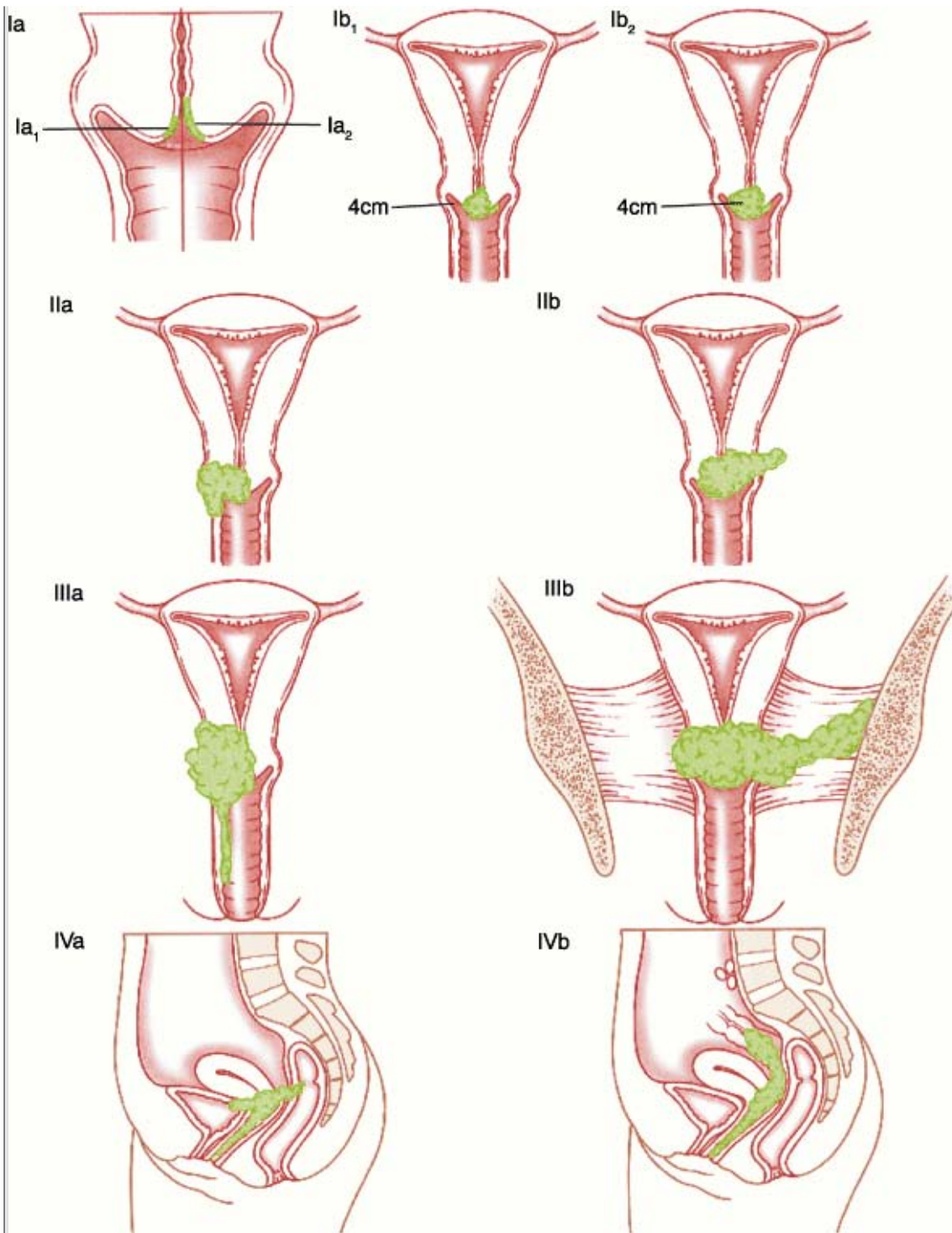


Figure 34.3 Carcinoma of the cervix uteri: staging cervical cancer (primary tumor and metastases). (From **Benedet JL, Odicino F, Maisonneuve P, et al.** Carcinoma of the cervix. *J Epidemiol Biostat* 2001;6:5–44, with permission.)

Additional Staging Modalities

Various investigators have used lymphangiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography (PET) in an attempt to improve the accuracy of clinical staging (12,13,14,15,16,17).

Table 34.2 Staging Procedures

Physical examination^a	Palpate lymph nodes
	Examine vagina
	Bimanual rectovaginal examination (under anesthesia recommended)
Radiologic studies^a	Intravenous pyelogram
	Barium enema
	Chest x-ray
	Skeletal x-ray
Procedures^a	Biopsy
	Conization
	Hysteroscopy
	Colposcopy
	Endocervical curettage
	Cystoscopy
	Proctoscopy
Optional studies^b	Computerized axial tomography
	Lymphangiography
	Ultrasonography
	Magnetic resonance imaging
	Positron emission tomography
	Radionucleotide scanning
	Laparoscopy

^aAllowed by the International Federation of Gynecology and Obstetrics (FIGO).

^bInformation that is not allowed by FIGO to change the clinical stage.

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Unfortunately, these modalities in general suffer from poor sensitivity and high false-negative rates. Evaluation of the para-aortic lymph nodes with lymphangiography is associated with a false-positive rate of 20% to 40% and a false-negative rate of 10% to 20% (12,13,14). Overall, lymphangiography has a sensitivity of 79% and specificity of 73% (18). Computed tomography has poor sensitivity (34%) but excellent specificity (97%) (18). The accuracy of CT scanning is 80% to 85%; the false-negative rate is 10% to 15%, and the false-positive rate is 20% to 25% (15,16,17). Ultrasound has a high false-negative rate (30%), low sensitivity (19%), but high specificity (99%) (18). Early MRI data showed that MRI results were comparable to those of CT scanning (19), a finding confirmed on meta-analysis (20). However, **a recent systematic review comparing CT scan with MRI has shown that MRI is significantly more sensitive with equivalent specificity.** Additionally, MRI has excellent sensitivity on T2-weighted images for the detection of parametrial disease (21). As a result, MRI has become the preferred study to evaluate tumor size, lymph node metastasis, and local tumor extension.

Position emission tomography scans are increasingly being utilized either alone or in conjunction with CT or MRI to detect metastatic disease; however, large prospective data series are limited. Early studies suggest that PET may be more useful than other techniques for the detection of abdominal and extrapelvic disease, with comparable or better sensitivity (76%–100%) and specificity (94%) (22,23). In addition, PET scans may be a better predictor of treatment outcome. Although early studies show promise for the use of PET

P.1411

scans in evaluating cervical cancer, the sensitivity for detecting metastatic disease less than 1 cm in size appears to be limited (24).

When abnormalities are noted on CT, MRI, or PET, radiographic guided fine-needle aspirations (FNA) can be performed to confirm metastatic disease and individualize treatment planning. Because these tests are not generally available throughout the world and the interpretation of results can be variable, these studies are not currently used for staging. They may, however, be useful in individual treatment planning.

The clinical staging system developed by FIGO is based on the belief that cervical cancer is a local disease until rather late in its course. Unfortunately, **the accuracy of clinical staging is limited, and surgical evaluation, although not practical or feasible in all patients, can more accurately identify metastatic disease.** Surgical staging has been advocated by providers who believe that surgical information details the extent of disease, allowing the treatment to be tailored to the individual (25). However, other providers believe that surgical staging should be limited to patients who are enrolled in clinical trials. These beliefs are based on the lack of randomized controlled studies demonstrating a survival benefit in patients who have had surgical staging.

Pathology

Squamous Cell Carcinoma

Invasive squamous cell carcinoma is the most common variety of invasive cancer in the cervix. Histologically, variants of squamous cell carcinoma include **large cell keratinizing, large cell nonkeratinizing, and small cell types** (26). Large cell keratinizing tumors consist of tumor cells forming irregular infiltrative nests with laminated keratin pearls in the center. Large cell nonkeratinizing carcinomas reveal individual cell keratinization but do not form keratin pearls (Fig. 34.4). The category of small cell carcinoma

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includes poorly differentiated squamous cell carcinoma and small cell anaplastic carcinoma. If possible, these two tumors should be differentiated. The former contains cells that have small-to medium-sized nuclei and more abundant cytoplasm than those of the latter. The designation of small cell anaplastic carcinoma should be reserved for lesions resembling oat cell carcinoma of the lung. Small cell anaplastic carcinoma infiltrates diffusely and consists of tumor cells that have scanty cytoplasm, round to oval small nuclei, coarsely granular chromatin, and high mitotic activity. The nucleoli are absent or small. **Immunohistochemistry or electron microscopy can differentiate the small cell neuroendocrine tumors.** Patients with the large cell type of carcinoma, with or without keratinization, have a better prognosis than those with the small cell variant. Furthermore, small cell anaplastic carcinomas behave more aggressively than poorly differentiated squamous carcinomas that contain small cells. Infiltration of parametrial tissue and pelvic lymph node metastasis affect the prognosis.

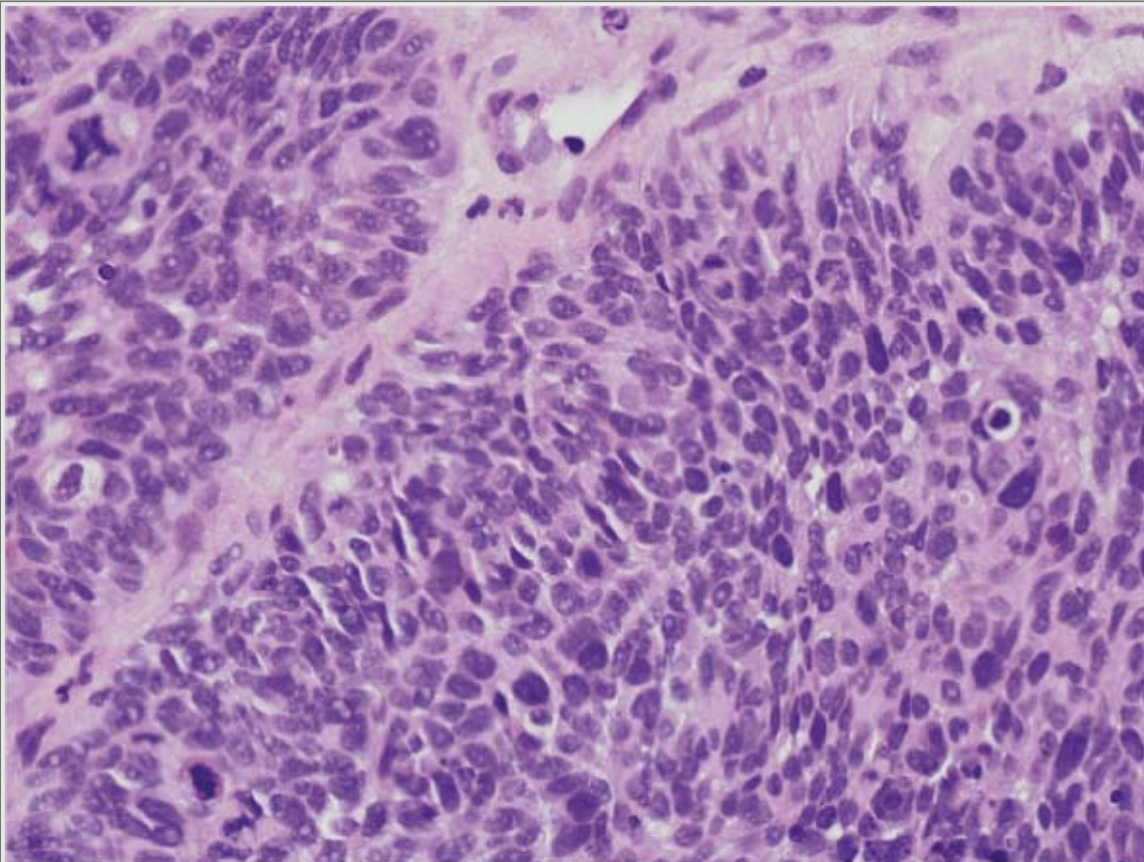


Figure 34.4 Invasive squamous cell carcinoma, large cell nonkeratinizing type. Tumor cells form irregular nests and have abundant eosinophilic cytoplasm and distinct cell borders indicative of squamous differentiation.

Other less common variants of squamous carcinoma include **verrucous carcinoma** and **papillary (transitional) carcinoma**. Verrucous carcinomas may resemble giant condyloma acuminatum, are locally invasive, and rarely metastasize. Papillary carcinomas histologically resemble transitional cells of the bladder and may have more typical squamous cell invasion at the base of the lesion. Papillary carcinomas behave and are treated in a manner similar to traditional squamous cell cancers, except that late recurrences have been noted.

Adenocarcinoma

In recent years, there has been an increasing number of cervical adenocarcinomas reported in women in their 20s and 30s. Although the total number of cases of adenocarcinoma has been relatively stable, this disease is being seen with increasing frequency in young women, especially as the number of cases of invasive squamous cell carcinoma decreases. Older reports indicated that 5% of all cervical cancers were adenocarcinomas (27), whereas newer reports show a proportion as high as 18.5% to 27% (28,29).

Adenocarcinoma *in situ* (AIS) is believed to be the precursor of invasive adenocarcinoma, and it is not surprising that the two often coexist (30). In addition to AIS, intraepithelial or invasive squamous neoplasia occurs in 30% to 50% of cervical adenocarcinomas (31). A squamous intraepithelial lesion may be observed colposcopically on the ectocervix and the coexistent adenocarcinoma often is higher in the cervical canal.

Patients with AIS who are treated with conization should undergo close clinical follow-up. Endocervical curettage, often used in surveillance, may miss residual or invasive disease, and false-negative rates as high as 50% have been reported (32). In addition, skip lesions not resected at the time of conization may be present. For these reasons, hysterectomy should be considered the standard therapy for patients who have completed their childbearing. In two reports, however, patients with negative cone biopsy margins were followed conservatively, with few requiring repeat surgical procedures (33,34). Because cervical AIS tends to affect women during their reproductive years, a thorough discussion of risks and benefits should take place, and treatment should be individualized.

Adenocarcinoma of the cervix is managed in the same a manner to that used for squamous cell carcinoma. Previously, it was believed that adenocarcinoma was associated with a worse prognosis and outcome when compared with squamous cell carcinoma. A study of 203 women with adenocarcinoma and 756 women with squamous carcinoma supported this assertion (29). This study showed 5-year survival rates of 90% versus 60%, 62% versus 47%, and 36% versus 8% for stages I, II, and III, respectively. Although some have attributed these rates to a relative resistance to radiation, they are more likely a reflection of the tendency of adenocarcinomas to grow endophytically and to be undetected until a large volume of tumor is present. When adjusted for stage, however, it now appears that

P.1413

P.1414

there is no difference in prognosis between the two histologic subtypes. Adenocarcinoma may be detected by cervical sampling, but less reliably so than squamous carcinomas. A definitive diagnosis may require cervical conization.

The clinical features of stage I adenocarcinomas have been well studied (28,35,36,37). These studies have identified size of tumor, depth of invasion, grade of tumor, and age of the patient as significant correlates of lymph node metastasis and survival. When matched with squamous carcinomas for lesion size, age, and depth of invasion, the incidence of lymph node metastases and the survival rate appear to be the same (36,37). **Patients with stage I adenocarcinomas can be selected for treatment according to the same criteria as for those with squamous cancers** (36).

The choice of treatment for bulky stage I and II tumors is controversial. Treatment with radiation alone has been advocated by some (38), whereas others support radiation plus extrafascial hysterectomy (39,40). In 1975, Rutledge et al. (39) reported an 85.2% 5-year survival rate for all patients with stage I disease treated with radiation alone and an 83.8% survival rate for those who had radiation plus surgery. The central persistent disease rate was 8.3%, compared with 4% for those who had radiation plus surgery. In stage II disease, the 5-year survival rate was 41.9% for radiation alone and 53.7% for radiation plus surgery. **A subsequent report revealed no significant difference in survival among patients treated with radiation alone or radiation plus extrafascial hysterectomy** (41).

Invasive adenocarcinoma may be pure (Fig. 34.5A and B) or mixed with squamous cell carcinoma. Within the category of pure adenocarcinoma, the tumors are quite heterogeneous (26), with a wide range of cell types, growth patterns, and differentiation. **About 80% of cervical adenocarcinomas are made up predominantly of cells of the endocervical type with mucin production. The remaining tumors are populated by endometrioid cells, clear cells, intestinal cells, or a mixture of more than one cell type. By histologic examination alone, some of these tumors are indistinguishable from those arising elsewhere in the endometrium or ovary.** Within each cell type, the growth patterns and nuclear abnormalities vary according to the degree of differentiation. In well-differentiated tumors, tall columnar cells line the well-formed branching glands and

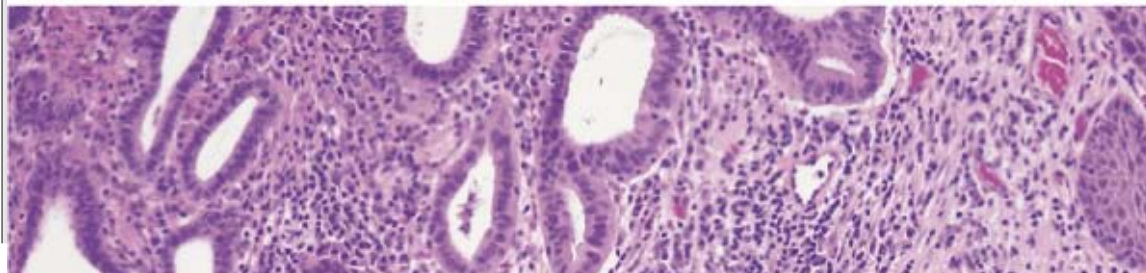
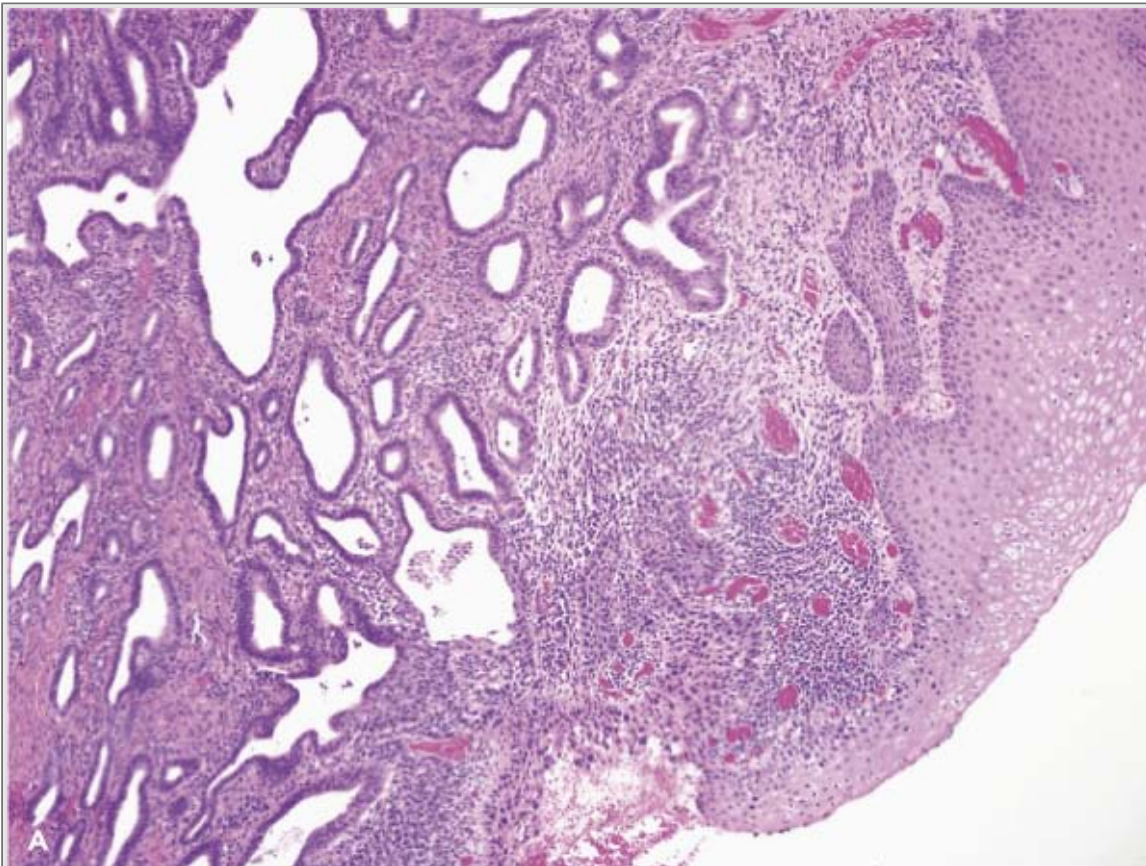
papillary structures, whereas pleomorphic cells tend to form irregular nests and solid sheets in poorly differentiated neoplasms. The latter may require mucicarmine and periodic acid—Schiff (PAS) staining to confirm their glandular differentiation.

There are several special variants of adenocarcinoma. **Minimal deviation**

adenocarcinoma (adenoma malignum) is an extremely well-differentiated form of adenocarcinoma in which the branching glandular pattern strongly simulates that of the normal endocervical glands. In addition, the lining cells have abundant mucinous cytoplasm and uniform nuclei (42,43). Because of this, the tumor may not be recognized as malignant in small biopsy specimens, thereby causing considerable delay in diagnosis.

Special immunohistochemical staining may be required to establish the diagnosis. Earlier studies reported a dismal outcome for women with this tumor, but more recent studies have found a favorable prognosis if the disease is detected early (44). Although rare, similar tumors have also been reported in association with endometrioid, clear, and mesonephric cell types (45).

An entity described as **villoglandular papillary adenocarcinoma** also deserves special attention (46). It primarily affects young women, some of whom are pregnant or users of oral contraceptives. Histologically, the tumors have smooth, well-defined borders, are well differentiated, and are either *in situ* or superficially invasive. Follow-up information is encouraging. None of these tumors has recurred after cervical conization or hysterectomy, and no metastasis has been detected among women undergoing pelvic nodal dissection. This tumor appears to have limited risk for spread beyond the uterus.



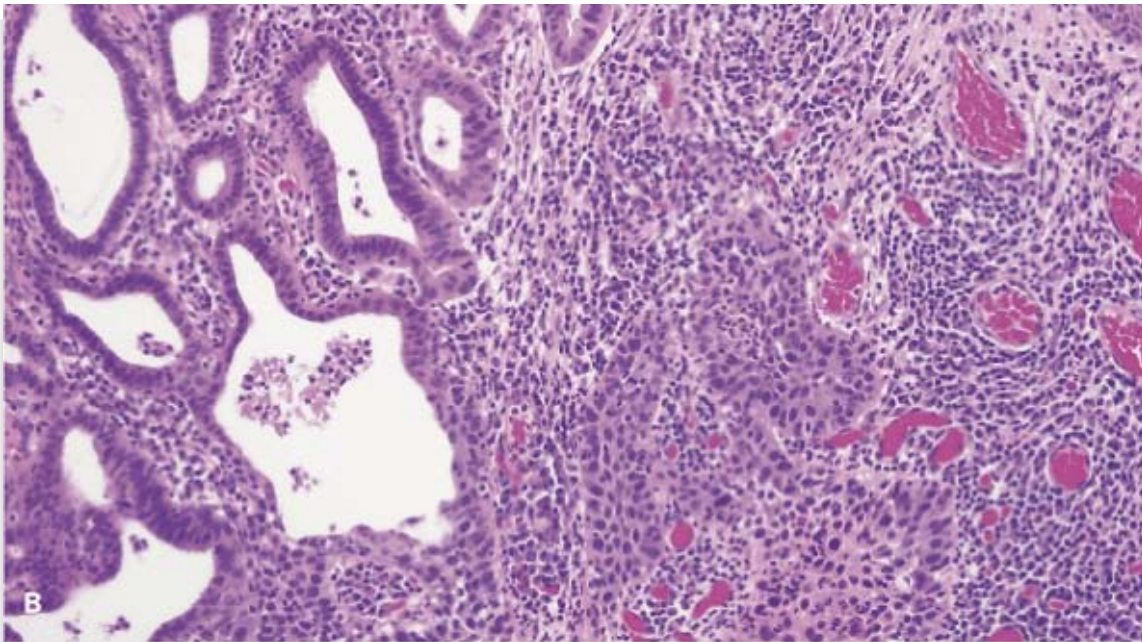


Figure 34.5A and B Invasive adenocarcinoma of the cervix, well-differentiated. Irregular glands are lined with tall columnar cells with vacuolated mucinous cytoplasm resembling endocervical cells. Nuclear stratification, mild nuclear atypism, and mitotic figures are evident.

P.1415

Adenosquamous Carcinoma

Carcinomas with a mixture of malignant glandular and squamous components are known as **adenosquamous carcinomas**. Patients with adenosquamous carcinoma of the cervix have been reported to have a poorer prognosis than those with pure adenocarcinoma or squamous carcinoma (47). Whether this is true when corrected for size of lesion is controversial (35,36).

In mature adenosquamous carcinomas, the glandular and squamous carcinomas are readily identified on routine histologic evaluation and do not cause diagnostic problems. In poorly differentiated or immature adenosquamous carcinomas, however, glandular differentiation can be appreciated only with special stains, such as mucicarmine and PAS. In one study (45), 30% of squamous cell carcinomas demonstrated mucin secretion when stained with mucicarmine. These squamous cell carcinomas with mucin secretion have a higher incidence of pelvic lymph node metastases than do squamous cell carcinomas without mucin secretion (45), and they are similar to the signet-ring variant of adenosquamous carcinoma (48).

Glassy cell carcinoma has been recognized as a poorly differentiated form of adenosquamous carcinoma (48). Individual cells have abundant eosinophilic, granular, ground-glass cytoplasm, large round to oval nuclei, and prominent nucleoli. The stroma is infiltrated by numerous lymphocytes, plasma cells, and eosinophils. Approximately half of these tumors contain glandular structures or stain positive for mucin. The poor diagnosis of this tumor is linked to understaging and resistance to radiotherapy.

Other variants of adenosquamous carcinoma include **adenoid basal carcinoma** and **adenoid cystic carcinoma**. Adenoid basal carcinoma simulates the basal cell carcinoma of the skin (49). Nests of basaloid cells extend from the surface epithelium deep into the underlying tissue. Cells at the periphery of tumor nests form a distinct parallel nuclear arrangement, so-called peripheral palisading. An "adenoid" pattern occasionally develops, with "hollowed-out" nests of cells. Mitoses are rare, and the tumor often extends deep into the cervical stroma.

Adenoid cystic carcinoma of the cervix behaves much like such lesions elsewhere in the body. The tumors tend to invade into the adjacent tissues and metastasize late, often 8 to 10 years after the primary tumor has been removed. Like other adenoid cystic tumors, they may metastasize directly to the lung. The pattern simulates that of the adenoid basal tumor, but there is a cystic component, and the glands of the cervix are involved (49). Mitoses may be seen but are not numerous.

Sarcoma

The most important sarcoma of the cervix is **embryonal rhabdomyosarcoma**, which occurs in children and young adults. The tumor has grapelike polypoid nodules, known as botryoid sarcoma, and the diagnosis depends on the recognition of rhabdomyoblasts (50). **Leiomyosarcomas** and **mixed mesodermal tumors** involving the cervix may be primary but are more likely to be secondary to uterine tumors. **Cervical adenosarcoma** has been described as a low-grade tumor with a good prognosis (50). If recurrence develops, it is generally a central recurrence that may be treated with resection and hormonal therapy.

Malignant Melanoma

On rare occasions, melanosis has been seen in the cervix. Thus, **malignant melanoma** may arise de novo in this area. Histopathologically, it simulates melanoma elsewhere, and the prognosis depends on the depth of invasion into the cervical stroma.

Neuroendocrine Carcinoma

The classification of neuroendocrine cervical carcinoma includes four histologic subtypes: **(i) small cell, (ii) large cell, (iii) classical carcinoid, and (iv) atypical carcinoid** (51).

P.1416

Neuroendocrine tumors of the cervix are rare, and treatment regimens have been based on small case series of patients.

Small cell (neuroendocrine type) carcinoma of the cervix is aggressive in nature and is similar to cancer arising from the bronchus (52). The hallmark of neuroendocrine tumors is their aggressive malignant behavior with the propensity to metastasize. At the time of diagnosis, it is usually disseminated, with bone, brain, liver, and bone marrow being the most common sites of metastases. In one study of 11 patients with disease apparently confined to the cervix, a high rate of lymph node metastasis was noted (53). Pathologically, the diagnosis is aided by the finding of neuroendocrine granules on electron microscopy as well as by immunoperoxidase studies that are positive for a variety of neuroendocrine proteins such as calcitonin, insulin, glucagon, somatostatin, gastrin, and adrenocorticotrophic hormone (ACTH). In addition to the traditional staging for cancer of the cervix, these patients should undergo bone, liver, and brain scanning as well as bone marrow aspiration and biopsy to evaluate the possibility of metastatic disease. Therapy generally consists of surgery, chemotherapy, and radiation. Because patients with early-stage disease have distant metastases, multimodal therapy is recommended. The main active chemotherapeutic agent is *etoposide*.

Local therapy alone gives almost no chance of cure of small cell carcinoma. Regimens of combination chemotherapy have improved the median survival rates in small cell bronchogenic carcinoma, and these regimens are now being used for treatment of small cell carcinoma of the cervix. Combination chemotherapy may consist of *vincristine, doxorubicin, and cyclophosphamide* (VAC) or *VP-16 (etoposide) and cisplatin* (EP) (54). Patients must be monitored carefully because they are at high risk for developing

recurrent metastatic disease (55).

Patterns of Spread

Cancer of the cervix spreads by (i) direct invasion into the cervical stroma, corpus, vagina, and parametrium; (ii) lymphatic metastasis; (iii) blood-borne metastasis; and (iv) intraperitoneal implantation. The incidence of pelvic and para-aortic nodal metastasis is shown in Table 34.3.

The cervix is commonly involved in cancer of the endometrium and vagina. The latter is rare, and most lesions that involve the cervix and vagina are designated **cervical primaries**. Consequently, the clinical classification is that of cervical neoplasia extending to the vagina, rather than vice versa. Endometrial cancer may extend into the cervix by three modes: direct extension from the endometrium, submucosal involvement by lymph

P.1417

vascular extension, and multifocal disease. The latter is most unusual, but occasionally a focus of adenocarcinoma may be seen in the cervix, separate from the endometrium. This lesion should not be diagnosed as metastasis but rather as multifocal disease. Malignancies involving the peritoneal cavity (e.g., ovarian cancer) may be found in the cul-de-sac and extend directly into the vagina and cervix. Carcinomas of the urinary bladder and colon occasionally extend into the cervix. Cervical involvement by lymphoma, leukemia, and carcinoma of the breast, stomach, and kidney is usually part of the systemic pattern of spread for these malignancies. Isolated metastasis to the cervix in such cases may be the first sign of a primary tumor elsewhere in the body.

Table 34.3 Incidence of Pelvic and Para-aortic Nodal Metastasis by Stage

Stage	No. of Patients	Positive Pelvic Nodes (%)	Positive Para-aortic Nodes (%)
Ia1 (≤3 mm)	179 ^a	0.5	0
Ia2 (>3–5 mm)	84 ^a	4.8	<1
Ib	1,926 ^b	15.9	2.2
IIa	110 ^c	24.5	11
IIb	324 ^c	31.4	19
III	125 ^c	44.8	30
IVa	23 ^c	55	40

^aReferences 72, 102, 106, 109, 110, 147
^bReferences 12, 72, 74, 82, 83, 86, 87, 88, 89, 90, 149
^cReferences 12, 13, 83, 86, 87, 91, 118

Treatment Options

The treatment of cervical cancer is similar to the treatment of any other type of malignancy in that both the primary lesion and potential sites of spread should be evaluated and treated. The therapeutic modalities for achieving this goal include primary treatment with surgery, radiotherapy, chemotherapy, or chemoradiation. **Whereas radiation therapy can be used in all stages of disease, surgery is limited to patients with stage I to IIa disease. The 5-year survival rate for stage I cancer of the cervix is approximately 85% with either radiation therapy or radical hysterectomy.** A recent study using the National Cancer Institute's Surveillance Epidemiology and End Results data showed by an intent-to-treat analysis that patients in the surgery arm had an improved survival when compared with patients in the radiation arm (56). In general, optimal therapy consists of radiation or

surgery alone to limit the increased morbidity that occurs when the two treatment modalities are combined. There have recently been great strides in the treatment of cervical carcinoma, including adjuvant chemoradiation in patients discovered to have high-risk cervical carcinoma after radical hysterectomy and in patients with locally advanced cervical carcinoma.

Surgery

There are advantages to the use of surgery instead of radiotherapy, particularly in younger women for whom conservation of the ovaries is important. Chronic bladder and bowel problems that require medical or surgical intervention occur in up to 8% of patients undergoing radiation therapy (57). Such problems are difficult to treat because they result from fibrosis and decreased vascularity. This is in contrast to surgical injuries, which in general are easily repaired and without long-term complications. Sexual dysfunction is less likely to occur after surgical therapy than radiation because of vaginal shortening, fibrosis, and atrophy of the epithelium associated with radiation. Surgical therapy shortens the vagina, but gradual lengthening can be brought about by sexual activity. The epithelium does not become atrophic because it responds either to endogenous estrogen or to exogenous estrogens if the patient is postmenopausal.

In general, radical hysterectomy is reserved for women who are in good physical condition. Advanced chronologic age should not be a deterrent. With improvements in anesthesia, elderly patients withstand radical surgery almost as well as their younger counterparts (58). **Generally, it is prudent not to operate on lesions that are larger than 4 cm in diameter because these patients will require postoperative radiation therapy.** When selected in this manner, the urinary fistula rate is less than 2% (59), and the operative mortality rate is less than 1% (60). A summary of the management of cervical cancer is presented in Table 34.4.

If radiation therapy is needed, ovarian function may be preserved by transposing the ovaries out of the planned radiation field. While transposition may provide some protection, some studies suggest that normal ovarian function is preserved in fewer than 50% of patients (61,62). Additionally, metastasis to the ovaries occurs in 0.5% of cases of squamous cell cancer and 1.7% of cases of adenocarcinomas of the cervix, so ovarian preservation at the time of surgery may incur a small risk (63).

Table 34.4 Management of Invasive Cancer of the Cervix

Stage Ia1	≤ 3 mm invasion, no LVSI	Conization or type I hysterectomy
	≤ 3 mm invasion, w/LVSI	Radical trachelectomy or type II radical hysterectomy with pelvic lymph node dissection
Ia2	$>3-5$ mm invasion	Radical trachelectomy or type II radical hysterectomy with pelvic lymphadenectomy
Ib1	>5 mm invasion, <2 cm	Radical trachelectomy or type III radical hysterectomy with pelvic lymphadenectomy
Ib2	>5 mm invasion, >2 cm	Type III radical hysterectomy with pelvic lymphadenectomy
	>5 mm invasion	Type III radical hysterectomy with pelvic and para-aortic lymphadenectomy or primary chemoradiation
Stage IIa		Type III radical hysterectomy with pelvic and para-aortic lymphadenectomy or primary chemoradiation
IIb, IIIa, IIIb		Primary chemoradiation

Stage IVA	Primary chemoradiation or primary exenteration
IVb	Primary chemotherapy \pm 6 radiation LVSI, lymphovascular space invasion.

Cone Biopsy of the Cervix

Cone biopsy of the cervix serves both a diagnostic and therapeutic role in cervical cancer. The procedure is indicated to confirm the diagnosis of cancer, as well as to definitively treat stage Ia1 disease when preservation of fertility is desired. For effective treatment, there must be no evidence of lymph—vascular space invasion, and both endocervical margins and curettage findings must be negative for cancer or dysplasia. Because stage Ia1 cancers have less than a 1% risk of lymph node metastasis, lymphadenectomy is not necessary. If the endocervical margin or curettage is positive for dysplasia or malignancy, further treatment is necessary as these findings are strong predictors of residual disease. For squamous cell carcinoma, the risk of residual disease is 4% if both the endocervical margin and curettage are negative for dysplasia or malignancy, 22% if the endocervical margin alone is positive, and 33% if both are positive (64). In cases of adenocarcinoma in situ, the status of the cone margins is particularly important, with residual preinvasive and invasive disease noted in up to 25% and 3%, respectively, of cases with negative margins, and up to 80% and 7%, respectively, in cases with positive margins (65,66).

Simple (Extrafascial) Hysterectomy

Type I hysterectomy is an appropriate therapy for patients with stage Ia1 tumors without lymph—vascular space invasion who are not desirous of future fertility. In such cases, lymphadenectomy is not recommended. If lymph—vascular space invasion is found, a modified radical hysterectomy with pelvic lymphadenectomy is appropriate and effective therapy.

Radical Trachelectomy

Radical trachelectomy is a procedure that is gaining popularity as a surgical management option for women with stage 1a2 and 1b1 disease who desire uterine preservation and fertility. This procedure may be performed vaginally or abdominally (Fig. 34.6), and it usually is accompanied by pelvic lymphadenectomy and cervical cerclage placement. The risk of positive pelvic lymph nodes with stage 1a2 cancer may be as high as 8%, indicating the need for lymphadenectomy. Lymphadenectomy may be performed either laparoscopically or by the open laparotomy technique. Experience with this therapeutic modality is limited, and it is uncertain if long-term outcome is similar to that of

traditionally therapy, although early results are promising. **Patients who are ideal candidates for this procedure have tumors less than 2 cm in diameter, negative lymph nodes, and no lymph—vascular space involvement.** There are limited data on subsequent pregnancy outcomes after radical trachelectomy; however, successful outcomes have been reported. In one study, there were 102 pregnancies and 65 live births in 92 women who had radical trachelectomy. Increased rates of preterm birth, preterm premature rupture of membranes, and miscarriages have been noted. (67,68).

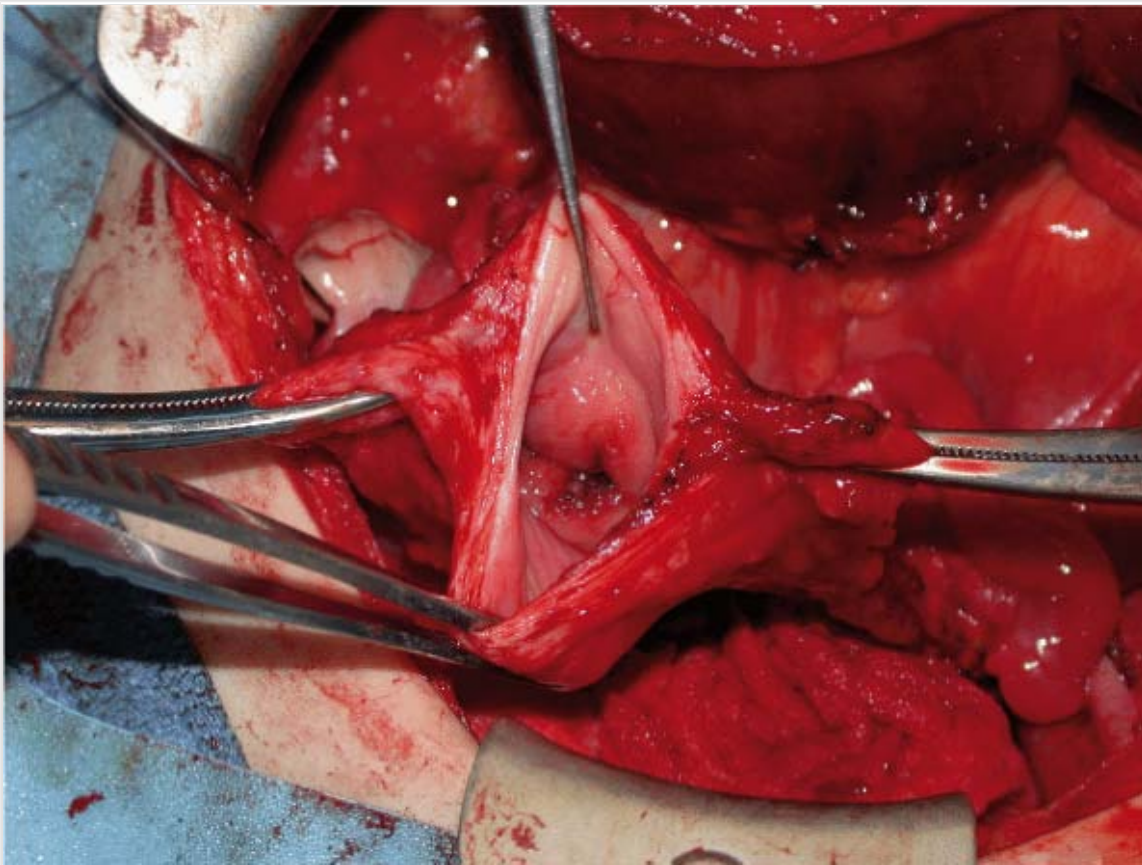


Figure 34.6 Abdominal radical trachelectomy.

Although radical trachelectomy and lymphadenectomy are performed with curative intent, it should be remembered that the risk of recurrence after such procedures depends on risk factors being well-defined. If recurrence develops, definitive therapy with surgery or radiation is necessary.

Radical Hysterectomy

The **radical hysterectomy** (Fig. 34.7A and B) performed most often in the United States is that described by Meigs in 1944 (69). **The operation includes pelvic lymph node dissection along with removal of most of the uterosacral and cardinal ligaments and the upper one third of the vagina. This operation has been referred to as the type III radical hysterectomy (70).**

The **hysterectomy described by Wertheim is less extensive than a radical hysterectomy and removes the medial half of the cardinal and uterosacral ligaments (70). This procedure is often referred to as the modified radical or type II hysterectomy.** Wertheim's original operation did not include pelvic lymph node dissection but instead included selective removal of enlarged lymph nodes. **The modified radical hysterectomy (type II) differs from the radical hysterectomy (type III) in the following ways:**

- The uterine artery is transected at the level of the ureter, thus preserving the ureteral branch to the ureter.

- The cardinal ligament is not divided near the sidewall but instead is divided at about its midportion near the ureteral dissection.
- The anterior vesicouterine ligament is divided, but the posterior vesicouterine ligament is conserved.
- A smaller margin of vagina is removed.

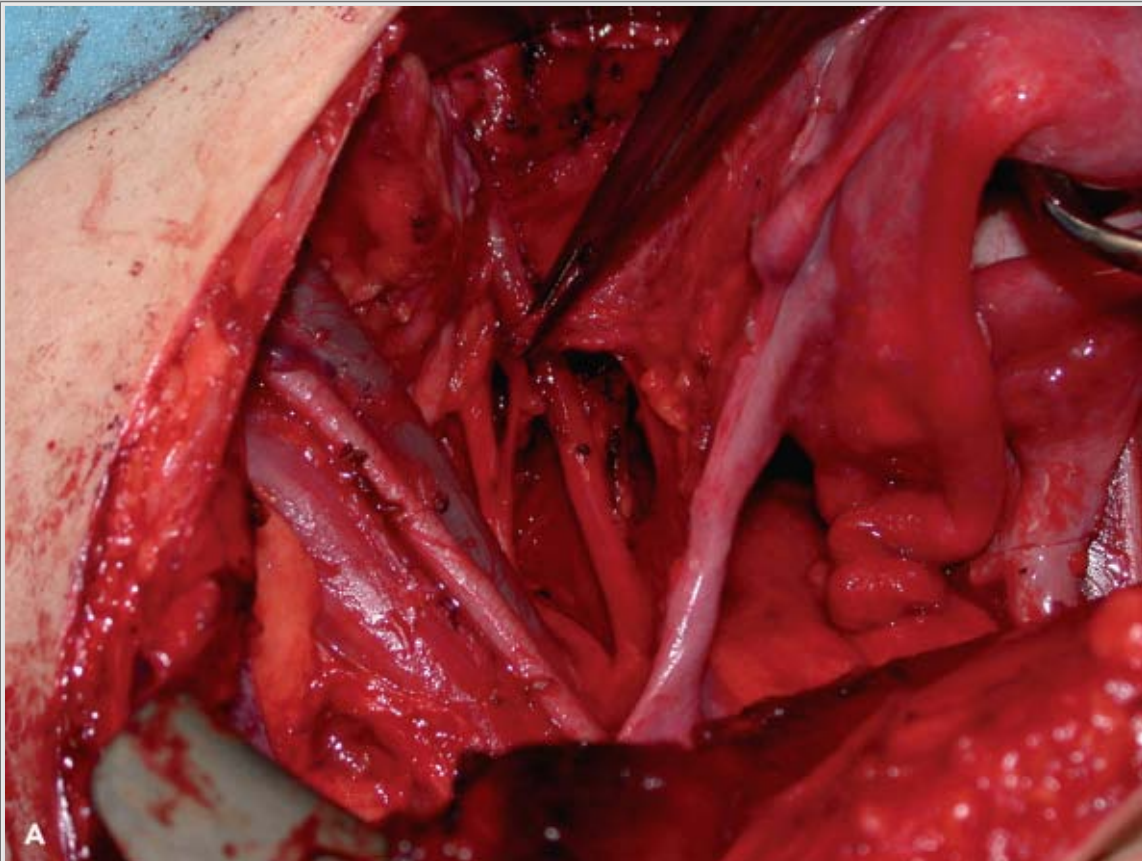


Figure 34.7A Radical hysterectomy. An intraoperative photograph showing the lateral dissection during a radical hysterectomy. Note the ureter running beneath the uterine artery (tissue in the clamp).



Figure 34.7B Radical hysterectomy specimen.

Radical hysterectomies can be further classified as extended radical hysterectomy (type IV and type V). In the type IV operation, the periureteral tissue, superior vesicle artery, and as much as three fourths of the vagina are removed (70). In the type V operation, portions of the distal ureter and bladder are resected. This procedure is rarely performed because radiotherapy should be used when such extensive disease is encountered (70).

The abdomen is opened through either a midline incision or a low transverse incision after the methods of Maylard or Cherney. The low transverse incision requires division of the rectus muscles and provides excellent exposure of the lateral pelvis. It allows adequate pelvic node dissection and wide resection of the primary tumor. After the abdomen is entered, the peritoneal cavity is explored to exclude metastatic disease. The stomach is palpated to ensure that it has been decompressed to facilitate packing of the intestines. The liver is palpated, and the omentum is inspected for metastases. Both kidneys are palpated to ensure their proper placement and lack of congenital and other abnormalities. The para-aortic nodes are palpated transperitoneally.

During exploration of the pelvis, the fallopian tubes and ovaries are inspected for any abnormalities. **In premenopausal patients, the ovaries are generally conserved.** The peritoneum of the vesicouterine fold and the rectouterine pouch should be inspected for signs of tumor extension or implantation. The cervix is then palpated between the thumb anteriorly and the fingers posteriorly to determine its extent, and the cardinal ligaments are palpated for evidence of lateral tumor extension or nodularity.

Lymphadenectomy

After inspection of the abdomen and pelvis, the pelvic and para-aortic lymph nodes should be inspected and palpated. Lymph nodes suspicious for gross disease should

be excised and evaluated by frozen section. If metastatic disease is identified, consideration should be given to abandoning radical surgery in favor of primary chemoradiation therapy. If the patient has no gross evidence of metastatic disease, the pelvic lymphadenectomy is begun.

Pelvic Lymphadenectomy

The pelvic lymph node dissection is begun by opening the round ligaments at the pelvic sidewall and developing the paravesical and pararectal spaces. The ureter is elevated on the medial flap by a Deaver retractor to expose the common iliac artery. The common iliac and external iliac nodes are dissected, with care taken to avoid injuring the genitofemoral nerve, which lies laterally on the psoas muscle. At the bifurcation of the common iliac artery, the external iliac node chain is divided into lateral and medial portions.

The lateral chain is stripped free from the artery to the circumflex iliac vein distally. A hemaclip is placed across the distal portion of the lymph node chain to reduce the incidence of lymphocyst formation. The medial chain is then dissected. The obturator lymph nodes are dissected next; for this procedure, the lymph nodes are grasped just under the external iliac vein, and traction is applied medially. Although in most patients both the obturator artery and vein are dorsal to the obturator nerve, 10% have an aberrant vein arising from the external iliac vein. The node chain is separated from the nerve and vessels and clipped caudally. Dissection continues cephalad to the hypogastric artery. The cephalad portion of the obturator space should be entered lateral to the external iliac artery and

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medial to the psoas muscle, where the remainder of the obturator node tissue can be dissected as far cephalad as the common iliac artery. In general, drainage of the pelvic and para-aortic lymph node beds is not performed because of the increase in complications in patients in whom drains have been used (71).

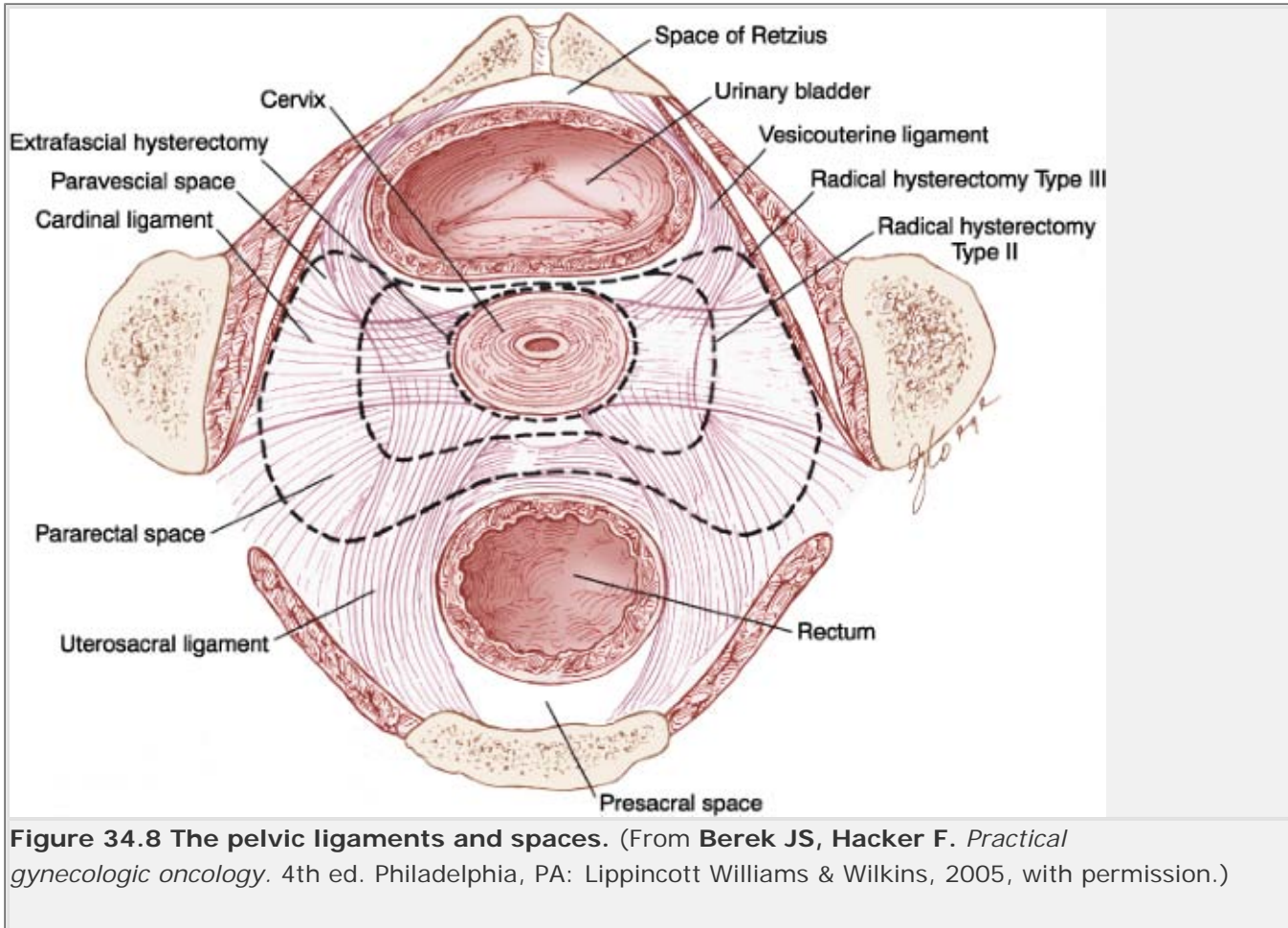
Patients who have bulky cervical tumors or grossly positive pelvic nodes, or for whom frozen section evaluation will be performed, should then undergo para-aortic lymph node evaluation to determine the full extent of disease and to guide adjuvant therapy.

Para-aortic Lymph Node Evaluation

The bowel is packed to expose the peritoneum overlying the bifurcation of the aorta. The peritoneum is incised medial to the ureter and over the right common iliac artery. A retractor is placed retroperitoneally to expose the aorta and the vena cava. Any enlarged para-aortic lymph nodes are removed, hemaclips are applied for hemostasis, and specimens are sent for analysis by frozen section. If the lymph nodes are positive for metastatic cancer, an option is to discontinue the operation and treat the patient with radiation therapy (69). If the lymph nodes are negative for disease, the left side of the aorta is palpated through the peritoneal incision with a finger passed under the inferior mesenteric artery. The lymph nodes on this side of the aorta are more lateral and nearly behind the aorta and the common iliac artery. If the left para-aortic lymph nodes appear healthy and the cervical tumor is small with no suspicious pelvic lymph nodes, these additional lymph nodes are not submitted for frozen-section analysis. If they are removed, they may be dissected through the incision made for the right para-aortic nodes, or they may be dissected after reflection of the sigmoid colon medially.

Development of Pelvic Spaces

The pelvic spaces are developed by sharp and blunt dissection (Fig. 34.8).



The paravesical space is bordered by the following structures:

- The obliterated umbilical artery running along the bladder medially
- The obturator internus muscle along the pelvic sidewall laterally
- The cardinal ligament posteriorly
- The pubic symphysis anteriorly

The attachments of the vagina to the tendinous arch form the floor of the paravesical space.

The pararectal space is bordered by the following structures:

- The rectum medially
- The cardinal ligament anteriorly

- **The hypogastric artery laterally**
- **The sacrum posteriorly**

The coccygeus (levator ani) muscle forms the floor of the pararectal space.

The development of these spaces before pelvic lymphadenectomy will aid in identification and dissection of the pelvic lymph nodes as well as dissection of the ureter as it passes into the vesicouterine ligament tunnel.

Dissection of the Bladder

The dissection of the bladder from the anterior part of the cervix and vagina is a critical step. Occasionally, tumor extension into the base of the bladder (which cannot be detected with cystoscopy) precludes adequate mobilization of the bladder flap, leading to the abandonment of the operation. Therefore, this portion of the operation should be undertaken early in the procedure. The bladder should be mobilized off of the upper third of the vagina to remove the tumor safely and with adequate margins.

Dissection of the Uterine Artery

The superior vesicle artery is dissected away from the cardinal ligament at a point near the uterine artery. **The uterine artery, which usually arises from the superior vesicle artery, is thus isolated and divided, preserving the superior vesicle arteries.** The uterine vessels are then brought over the ureter by application of gentle traction. Occasionally, the uterine vein passes under the ureter.

Dissection of the Ureter

The ureter is dissected free from the medial peritoneal flap at the level of the uterosacral ligament. As the ureter passes near the uterine artery, there is a consistent arterial branch from the uterine artery to the ureter. This branch is sacrificed in the standard radical (type III) hysterectomy but preserved in the modified radical (type II) hysterectomy. Dissection of the ureter from the vesicouterine ligament (ureteral tunnel) may now be accomplished. If the patient has a deep pelvis, ligation of the uterosacral and cardinal ligaments may be undertaken first to bring the ureteral tunnel dissection closer to the operator. The roof of the ureteral tunnel is the anterior vesicouterine ligament. It should be ligated and divided to expose the posterior ligament. **The posterior ligament is also divided in the radical (type III) hysterectomy but conserved in the modified radical (type II) hysterectomy.**

Posterior Dissection

The peritoneum across the cul-de-sac is incised, exposing the uterosacral ligaments. **The rectum is rolled free from the uterosacral ligaments, which**

are divided midway to the sacrum in a radical (type III) hysterectomy and near the rectum in the modified radical (type II) operation. This allows the operator to develop the cardinal ligament separate from the rectum. A surgical clamp is placed on the cardinal ligament at the lateral pelvic sidewall in a radical hysterectomy and at the level of

the ureteral bed in the modified radical procedure. A clamp is placed on the specimen side to maintain traction and to ensure that the full cardinal ligament is excised with the specimen. A right-angled clamp then is placed caudad to this clamp across the paravaginal tissues. A second paravaginal clamp is usually needed to reach the vagina.

The vagina is entered anteriorly, and a suitable margin of proximal vagina is removed with the specimen. More vaginal epithelium can be excised if necessary, depending on the previous colposcopic findings. The vaginal edge may be sutured in a hemostatic fashion and left open with a drain from the pelvic space or closed with a suction drain placed percutaneously. The ureteral fistula and pelvic lymphocyst rates from these two techniques are similar.

Complications of Radical Hysterectomy

Acute Complications

The acute complications of radical hysterectomy include (72):

- Blood loss (average, 0.8 liters)
- Ureterovaginal fistula (1%–2%)
- Vesicovaginal fistula (1%)
- Pulmonary embolus (1%–2%)
- Small bowel obstruction (1%)
- Febrile morbidity (25%–50%)

Febrile morbidity is most often caused by pulmonary infection (10%) and is seen frequently with pelvic cellulitis (7%) and urinary tract infection (6%). Wound infection, pelvic abscess, and phlebitis all occur in fewer than 5% of patients (73).

Subacute Complications

The subacute effects of radical hysterectomy are postoperative bladder dysfunction and lymphocyst formation. For the first few days after radical hysterectomy, bladder volume is decreased, and filling pressure is increased. The sensitivity to filling is diminished, and the patient is unable to initiate voiding. The cause of this dysfunction is unclear. It is important to maintain adequate bladder drainage during this time to prevent overdistention. Bladder drainage is usually accomplished with a suprapubic catheter. It is more comfortable for the patient and allows the physician to perform cystometrography and determine residual urine volume without the need for frequent catheterization. In addition, the patient is able to accomplish voiding trials at home by clamping the catheter, voiding, and releasing to check the residual urine level. Cystometrography may be performed 3 to 4 weeks after surgery. For the catheter to be discontinued, the patient must be able to sense the fullness of the bladder, initiate voiding, and void with a residual urine level of less than 75 to 100 mL. Otherwise, voiding trials should continue at home until these criteria can be fulfilled.

Lymphocyst formation occurs in fewer than 5% of patients (73), and the cause is uncertain. Adequate drainage of the pelvis after radical hysterectomy may be an important step in prevention. However, routine placement of retroperitoneal drains has not been shown to reduce this morbidity (71). Ureteral obstruction, partial venous obstruction, and thrombosis may occur from lymphocyst formation. Simple aspiration of the lymphocyst is generally not curative, but percutaneous catheters with chronic drainage may allow healing. If this treatment is unsuccessful, operative intervention with excision of a portion

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of the lymphocyst wall and placement of either large bowel or omentum into the lymphocyst should be performed.

Chronic Complications

The most common chronic effect of radical hysterectomy is bladder hypotonia or, in extreme instances, atony. This condition occurs in about 3% of patients, regardless of the method of bladder drainage used (74,75). It may be a result of bladder denervation and not simply a problem associated with bladder overdistention (76). Voiding every 4 to 6 hours, increasing intra-abdominal pressure with Credés maneuver, and intermittent self-catheterization may be used to manage bladder hypotonia.

Ureteral strictures are uncommon in the absence of postoperative radiation therapy, recurrent cancer, or lymphocyst formation (59). If the stricture is associated with lymphocyst formation, treatment of the lymphocyst usually alleviates the problem. Strictures that occur after radiation therapy should be managed with ureteral stenting. If a ureteral stricture is noted in the absence of radiotherapy or lymphocyst formation, recurrent carcinoma is the most common cause. A CT scan of the area of obstruction should be obtained and cytologic assessment by FNA should be performed if there is a target lesion to exclude carcinoma. If the results of these tests are negative, a ureteral stent may be placed to relieve the stricture. Close observation for recurrent carcinoma is necessary, and the diagnosis of recurrence may ultimately require laparotomy.

Nerve-Sparing Radical Hysterectomy

Nerve-sparing radical hysterectomies have been described in recent years in an attempt to diminish the bladder dysfunction, sexual dysfunction, and colorectal motility disorders commonly encountered after traditional radical hysterectomy.

Multiple techniques have been described involving the identification of the pelvic autonomic nerves at the sacral promontory followed by various surgical methods of nerve preservation as the nerves transit the cardinal ligaments. These techniques are promising and have been shown in small series to reduce postoperative bladder dysfunction (77,78).

Laparoscopic Radical Hysterectomy

Laparoscopic-assisted radical vaginal hysterectomy is being performed with increasing frequency in highly selected patients. In one large series of 200 women with stage Ia1–IIb cervical cancer treated with laparoscopic lymphadenectomy followed by radical vaginal hysterectomy, the authors found a 5-year survival rate comparable to patients treated with a similar abdominal approach and a comparable rate of intraoperative complications (79).

The use of laparoscopy in cervical cancer patients is appealing because it may lead to less blood loss, improved cosmetic results, shorter duration of hospitalization, and faster recovery.

Sentinel Lymph Node Evaluation

Sentinel lymph node detection has become an integral part of the management strategy for breast cancer and melanoma and is currently being investigated as a diagnostic tool in multiple human malignancies, including carcinoma of the cervix. The sentinel node is a specific lymph node (or nodes) that is the first to receive drainage from a malignancy and is a primary site of nodal metastasis. In theory, the presence or absence of metastatic disease in the sentinel node should reflect the status of the nodal basin as a whole. Thus, a negative sentinel lymph node would allow omission of lymphadenectomy of the involved nodal basin. Sentinel lymph nodes are detected through perilesional injection of radiolabeled technetium-99 or blue dye followed by intraoperative identification of the sentinel lymph nodes utilizing handheld gamma probes or visual identification of blue-stained nodes. These techniques are primarily applicable in patients with early-stage disease and

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clinically negative lymph nodes, in whom lymph node status may influence the extent of the procedure or the use of adjuvant treatment.

Although data utilizing sentinel lymph node detection techniques in cervical cancer are limited, several interesting conclusions can be drawn from completed studies. Sentinel nodes can be detected in 80% to 100% of cervical cancer patients and have been detected by both laparotomy and laparoscopic techniques with equivalent detection rates. A combination of dye and radiolabeled techniques appears to be superior for the detection of sentinel lymph nodes over either technique used alone. Test sensitivity of 65% to 87% can be expected with a 90% to 97% negative predictive value. The likelihood of detecting sentinel nodes may depend on the tumor volume, the time from injection to retrieval of the sentinel nodes, and the volume of dye or radiolabeled tracer injected. Sentinel node detection rates do not appear to be influenced by prior cold knife cone biopsy. False-negative results have been reported. **The role of sentinel node detection in cervix cancer is purely investigational at this time; although the technique is promising, complete lymphadenectomy, when indicated, remains the standard of care** (80).

Postoperative Management

Prognostic Variables for Early-Stage Cervical Cancer (Ia2–IIa)

The survival of patients with early-stage cervical cancer after radical hysterectomy and pelvic lymphadenectomy depends on the presence or absence of several intermediate and high-risk pathologic factors (72,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95).

Intermediate-risk factors for recurrent disease:

- **Large tumor size**
- **Cervical stromal invasion to the middle or deep one third**
- **Lymph—vascular space invasion**

High-risk factors for recurrent disease:

- **Positive or close margins**
- **Positive lymph nodes**
- **Microscopic parametrial involvement**

Patients treated with radical hysterectomy that have intermediate- or high-risk factors have a 30% and 40% risk, respectively, of recurrence within 3 years (96,97,98).

Lesion Size

Lesion size is an independent predictor of survival. Patients with lesions smaller than 2 cm have a survival rate of approximately 90%, and patients with lesions larger than 2 cm have a 60% survival rate (84). When the primary tumor is larger than 4 cm, the survival rate drops to 40% (82,93). An analysis of a Gynecologic Oncology Group prospective study of 645 patients showed a 94.6% 3-year disease-free survival rate for patients with occult lesions, 85.5% for those with tumors smaller than 3 cm, and 68.4% for patients with tumors larger than 3 cm (94).

Depth of Invasion

Patients in whom depth of invasion is less than 1 cm have a 5-year survival rate of approximately 90%, but the survival rate falls to 63% to 78% if the depth of invasion is more than 1 cm (72,94,98).

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Parametrial Spread

Patients with spread to the parametrium have a 5-year survival rate of 69%, compared with 95% when the parametrium is negative. When the parametrium is involved and pelvic lymph nodes are also positive, the 5-year survival rate falls to 39% to 42% (85,95).

Lymph—Vascular Space Involvement

The significance of the finding of lymph—vascular space involvement is somewhat controversial. Several reports have shown a 50% to 70% 5-year survival rate when lymph—vascular space invasion is present and a 90% 5—year survival rate when invasion is absent (72,84,88,99,100,101,102,103). Others have found no significant difference in survival if the study is controlled for other risk factors (93,94,104,105,106). Lymph—vascular space involvement may be a predictor of lymph node metastasis and not an independent predictor of survival.

Lymph Nodes

The most dependent variable associated with survival is the status of the lymph

nodes. Patients with negative nodes have an 85% to 90% 5-year survival rate (94,107), whereas the survival rate for those with positive nodes ranges from 20% to 74%, depending on the number of nodes involved and the location and size of the metastases (90,91,92,98,107,108,109).

Data on lymph node status can be summarized as follows:

- When the common iliac lymph nodes are positive, the 5-year survival rate is about 25%, compared with about 65% when only the pelvic lymph nodes are involved (99,110,111).
- Bilateral positive pelvic lymph nodes portend a less favorable prognosis (22%–40% survival rate) than unilateral positive pelvic nodes (59%–70%) (110,111).
- The presence of more than three positive pelvic lymph nodes is accompanied by a 68% recurrence rate, compared with 30% to 50% when three or fewer lymph nodes are positive (90,108).
- Patients in whom tumor emboli are the only findings in the pelvic lymph node have an 82.5% 5-year survival rate, whereas the survival rate is 62.1% and 54% with microscopic invasion and macroscopic disease, respectively (81).

Given the high risk of recurrent disease in surgically treated patients with early-stage cervical cancer who exhibit intermediate- or high-risk pathologic factors, adjuvant radiation or chemoradiation therapy should be considered.

Primary Radiation Therapy

Radiotherapy can be used to treat all stages of cervical cancer, with cure rates of about 70% for stage I, 60% for stage II, 45% for stage III, and 18% for stage IV (3).

A comparison of surgery and radiation for treatment of low-stage disease is shown in Table 34.5. Primary radiation treatment plans generally consist of a combination of external teletherapy to treat the regional lymph nodes and to decrease the tumor volume, and brachytherapy delivered by intracavitary applicators or interstitial implants to provide a treatment boost to the central tumor. Intracavitary therapy alone may be used in patients with early disease when the incidence of lymph node metastasis is negligible.

The treatment sequence depends on tumor volume. Stage Ib lesions smaller than 2 cm may be treated first with an intracavitary source to treat the primary lesion, followed by external therapy to treat the pelvic lymph nodes. Larger lesions require external radiotherapy first to shrink the tumor and to reduce the anatomic distortion caused by the cancer. Such

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a treatment strategy enables the therapist to achieve better intracavitary dosimetry. **The usual doses delivered are 7,000 to 8,000 cGy to point A (defined as 2 cm superior to the external cervical os and 2 cm lateral to the internal uterine canal) and 6,000 cGy to point B (defined as 3 cm lateral to point A),** limiting the bladder and rectal dosage to less than 6,000 cGy. To achieve this level, it is necessary to adequately pack the bladder and bowel away from the intracavitary source. Localization films and careful calculation of dosimetry are mandatory to optimize the dose of radiation and to reduce the incidence of bowel and bladder complications. Local control depends on delivering an adequate dose to the tumor from the intracavitary source.

Table 34.5 Comparison of Surgery versus Radiation for Stage Ib/IIa Cancer of the Cervix		
	<i>Surgery</i>	<i>Radiation</i>
Survival	85%	85%
Serious complications	Urologic fistulas 1%–2%	Intestinal and urinary strictures and fistulas 1.4%–5.3%
Vagina	Initially shortened, but may lengthen with regular intercourse	Fibrosis and possible stenosis, particularly in postmenopausal patients
Ovaries	Can be conserved	Destroyed
Chronic effects	Bladder atony in 3%	Radiation fibrosis of bowel and bladder in 6%–8%
Applicability	Best candidates are younger than 65 years of age, <200 lb, and in good health	All patients are potential candidates
Surgical mortality	1%	1% (from pulmonary embolism during intracavitary therapy)

Although brachytherapy has traditionally been prescribed using a low-dose rate technique, high-dose rate techniques are becoming more popular, and controversy currently exists over which technique is superior. Low-dose rates typically use Cs-137 as the source, whereas high-dose rates use Ir-192. Proponents of high-dose rate techniques argue that the exposure of radiation to medical personnel is less, ambulatory therapy is possible, and total treatment time is less. Advocates of low-dose rate techniques cite literature suggesting that complication rates are higher with higher-dose rate therapy. **Several published trials have shown that although there may be slight stage-related differences in survival between patients treated with low- and high-dose rate regimens, overall the techniques have comparable survival and complication rates** (112,113,114).

As noted, clinical staging is imprecise and fails to accurately predict disease extension to the para-aortic nodes in 7% of patients with stage Ib, 18% with stage IIb, and 28% with stage III disease (115). Such patients will have "geographic" treatment failures if standard pelvic radiotherapy ports are used. As a result, treatment plans for these patients are individualized based on CT scans and biopsies of the para-aortic lymph nodes for consideration of extended-field radiotherapy. The routine use of extended-field radiation for "prophylactic para-aortic radiation" without documentation of distant metastasis to the para-aortic nodes has been evaluated and is typically not practiced because of the increased enteric morbidity associated with this treatment modality.

Intensity Modulated Radiation Therapy

A relatively new method of providing external beam therapy, known as intensity modulated radiation therapy (IMRT), may be a significant therapeutic development. This technique uses computer-generated algorithms that accurately distinguish between target treatment volumes and normal tissue. The radiation beam intensity is then modulated to optimize the delivery of radiation to the specified treatment volume while sparing adjacent normal tissue. The result appears to be much more accurate treatment of

the tumor with minimal toxicity. Emphasizing this point is a recent study in 40 gynecologic

cancer patients in which IMRT was used. Excellent coverage of the planned treatment volume was obtained, with no patient suffering grade 3 toxicity, and only 60% of patients suffering grade 2 toxicity compared with a historical rate of 90% toxicity with conventional techniques (116). This technique is especially promising for treating cervical cancer because it allows higher doses to be delivered much more precisely, allowing patients who are unable to undergo brachytherapy because of pelvic anatomy and tumor geometry a chance for curative therapy. Studies utilizing IMRT in treating patients with cervical cancer are limited, but experience with this technique is increasing.

Adjuvant Radiation

In an effort to improve survival rates, postoperative radiotherapy has been recommended for patients with high- and intermediate-risk factors such as metastasis to pelvic lymph nodes (72,82,99,107), invasion of paracervical tissue (85,86), deep cervical invasion (117), or positive surgical margins (108,118). Although most authors agree that postoperative radiotherapy is necessary in the presence of positive surgical margins, the use of radiation in patients with other high-risk factors is controversial. Increasing evidence supports the use of adjuvant radiation, however. Particularly controversial but best studied is the use of radiation in the presence of positive pelvic lymph nodes. The rationale for treatment is the knowledge that pelvic lymphadenectomy does not remove all of the nodal and lymphatic tissue and subsequent radiotherapy can sterilize remaining cancer. The hesitancy to recommend postoperative radiotherapy relates to the significant rate of postradiation bowel and urinary tract complications (119). Most of the data currently available are retrospective. However, a randomized study by the Gynecologic Oncology Group comparing radiation with no further treatment for patients at high risk for recurrence with negative pelvic nodes revealed a 30% serious complication rate, 16% reoperation rate, and a 2% mortality rate as a result of treatment-related complications (120).

Based on retrospective studies, it appears that postoperative radiation therapy for positive pelvic nodes can decrease pelvic recurrence but does not improve 5-year actuarial survival rates. One multi-institutional study showed no difference in survival in patients with three or fewer positive pelvic nodes (59% versus 60%) (98). However, there seemed to be a benefit when radiotherapy was given to those with more than three positive nodes.

In a study of 60 pairs of irradiated and nonirradiated women matched for age, lesion size, number, and location of positive nodes after radical hysterectomy (121), no significant difference was found in projected 5-year survival rates (72% for surgery alone, 64% for surgery plus radiation). The proportion of recurrences confined to the pelvis was 67% in patients treated with surgery only and 27% in patients treated with postoperative radiation ($p = 0.03$). In a Cox regression analysis of 320 women who underwent radical hysterectomy, 72 of whom received postoperative radiation (91), there was a significant decrease in pelvic recurrence but no survival benefit. A multi-institutional retrospective study was performed of 185 women with positive pelvic nodes after radical hysterectomy, 103 of who received postoperative radiotherapy (93). Multivariate analysis disclosed that radiotherapy was not an independent predictor of survival, whereas age, lesion diameter, and number of positive nodes were found to influence survival. These authors concluded that additional treatment is needed to improve survival rates. Because survival is limited by distant recurrence, the addition of chemotherapy to postoperative radiotherapy has been proposed. A 75% disease-free survival rate was reported at 3 years in 40 high-risk patients given *cisplatin*, *vinblastine*, and *bleomycin* after radical hysterectomy, and a 46% disease-free survival rate was found in 79 comparable patients who refused treatment (122). Only 4 (11.8%) of 34 patients with positive pelvic nodes had recurrences, whereas disease recurred in 8 (33%) of 24 untreated patients

with positive nodes. An 82% rate of disease-free survival was reported at 2 years among 32 patients who were treated postoperatively with radiation therapy plus *cisplatin* and *bleomycin* (123).

The location of lymph node metastases is apparently relevant to postirradiation recurrence rates. When common iliac lymph nodes are involved, the survival rate drops to 20% (100). As the number of positive pelvic nodes increases, the percentage of positive common iliac and low para-aortic nodes increases (ie, 0.6% when pelvic lymph nodes are negative, 6.3% with one positive pelvic node, 21.4% with two or three positive nodes, and 73.3% with four or more positive nodes) (100). This information has been used to recommend extended-field radiotherapy to patients with positive pelvic lymph nodes in an attempt to treat undetected extrapelvic nodal disease (100). A 3-year disease-free survival rate of 85% occurred in patients with positive pelvic nodes, and a survival rate of 51% occurred in patients with positive common iliac nodes; these rates are better than the survival rates of 50% and 23%, respectively, for historical control groups receiving radiotherapy to the pelvis alone.

The Gynecologic Oncology Group reported the results of a randomized controlled trial on patients with cervical cancer treated by radical hysterectomy and found to have at least two of the following risk factors: capillary lymphatic space invasion, more than one third stromal invasion, and large tumor burden (121). A total of 277 patients were entered into the study, with 140 patients randomized to no further therapy and 137 patients randomized to adjuvant pelvic radiotherapy. **Patients with these risk factors who were treated postoperatively with radiation therapy had a statistically significant (47%) decrease in recurrent disease.** The study results have not had adequate follow-up to show a statistically significant decrease in mortality. The data, however, demonstrate improved survival rates. The morbidity with combination therapy was acceptable, with a low rate of enteric and urinary complications. A second Gynecologic Oncology Group study of patients with high-risk cervical cancer randomized patients to concurrent chemoradiation therapy or radiation therapy alone (96), as discussed below.

Concurrent Chemoradiation

Radiation therapy fails to achieve tumor control in 20% to 65% of patients with advanced cervical cancer. Chemotherapy, despite its relative lack of success in treating patients with cervical cancer, has been studied as neoadjuvant treatment in combination with surgery. **Concomitant use of chemotherapy and radiation has been studied extensively by the Gynecologic Oncology Group, and results of five randomized studies have been reported.** The concept of chemoradiation encompasses the benefits of systemic chemotherapy with the benefits of regional radiation therapy. Additionally, **the use of chemotherapy to sensitize cells to radiation therapy has been shown to improve local—regional control.** These new results have changed the way cervical cancer is treated in many medical centers.

An intergroup trial involving the Gynecologic Oncology Group, the Southwestern Oncology Group, and the Radiation Therapy Oncology Group evaluated postoperative chemoradiation therapy in patients with stage Ia2, Ib, or IIa cervical cancer who were found to have positive pelvic lymph nodes, positive parametrial extension, or positive vaginal margins at the completion of radical hysterectomy (123). A total of 243 patients were assessed in this trial, with 127 receiving chemoradiation (*cisplatin*, *5-FU*, radiation therapy) and 116 receiving radiation. **The results of this trial showed a statistically significant improvement in progression-free survival and overall survival at 43 months for the patients receiving concurrent chemoradiation.** The 4-year survival rates for the patients receiving

chemoradiation versus radiation alone were 81% and 71%, respectively. The toxicity levels in the two groups were acceptable, with a higher rate of hematologic toxicity in the concurrent chemoradiation arm. **This study showed that in patients with these high-risk factors after radical hysterectomy for stage Ia2, Ib, and IIa disease, chemoradiation is the postoperative treatment of choice.**

Concurrent chemoradiation was also evaluated in patients with advanced cervical carcinoma. Gynecologic Oncology Group protocol 85 was a prospective study that enrolled

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patients with stage IIb to IVa cervical cancer and compared concurrent chemoradiation (124). There were 177 patients treated with *cisplatin*, 5-FU, and radiation. These patients were compared with 191 patients treated with *hydroxyurea* and radiation. The median follow-up of patients who were alive at the time of the analysis was 8.7 years. Patients who received concurrent chemoradiation and were treated with *cisplatin* and 5-FU had a statistically significant improvement in progression-free interval and overall survival (122). Hematologic toxicity levels in the two groups were similar. **This study showed that *cisplatin*-based concurrent chemoradiation was a superior treatment when compared with *hydroxyurea* and concurrent radiation.**

Gynecologic Oncology Group protocol 120 was initiated to evaluate patients with negative para-aortic nodes and cervical carcinoma stage IIb to IVa treated with concurrent chemoradiation. The treatment arms in this study consisted of radiation plus weekly *cisplatin*; or *cisplatin*, 5-FU, and *hydroxyurea*; or *hydroxyurea*. There were 176 patients in the weekly *cisplatin* arm; 173 patients in the *cisplatin*, 5-FU, and *hydroxyurea* arm; and 177 patients in the *hydroxyurea* arm (125). The two treatment arms with *cisplatin*-based chemotherapy and radiation showed an improvement in progression-free interval and overall survival at a median follow-up of 35 months. The relative risks for progression of disease or death were 0.55 and 0.57, respectively, for patients treated with *cisplatin*-based chemotherapy and radiation, compared with the patients treated with *hydroxyurea* and radiation (126). **This study confirmed the findings of GOG 85 and again suggested that *cisplatin*-based concurrent chemoradiation is the treatment of choice for patients with advanced-stage cervical cancer.**

A third Gynecologic Oncology Group trial evaluated patients with stage Ib to IVa cervical cancer. Of the patients enrolled in this study, 70% had stage Ib or IIa disease (127). A total of 403 patients were enrolled and evaluated. The 5-year survival rates were 73% in patients treated with chemoradiation and 58% in patients treated with radiation therapy alone. The cumulative rates of disease-free survival at 5 years were 67% in patients treated with concurrent chemoradiation and 40% in patients treated with radiation therapy alone. Survival and progression-free intervals for patients receiving concurrent chemoradiation were significantly improved (127). **The results of this study suggested that chemoradiation is the treatment of choice for stage IIb to IVa disease and that those patients with stage Ib2 and IIa disease may also benefit from chemoradiation.**

A Gynecologic Oncology Group study of chemoradiation comparing concurrent *cisplatin* and radiation with radiation alone in patients with bulky Ib cervical cancer also included adjuvant hysterectomy after completion of the radiation (127). There were 183 patients assigned to the concurrent chemotherapy and radiation arm, and 186 patients treated with radiation alone. The median duration of follow-up was 36 months, with disease recurrence detected in 37% of the patients treated with radiation alone, compared with 21% who were treated with concurrent chemoradiation (126). The 3-year survival rates were 83% in the group who received concurrent chemoradiation and 74% in the group that received radiation alone (126). The study also included adjuvant hysterectomy after completion of radiation treatment. However, because the results did not show an improvement in survival

by using adjuvant hysterectomy, the authors concluded that adjuvant hysterectomy would not be part of their recommendations. **This study supported the results of previous studies and showed that patients with bulky stage Ib and IIa cervical cancer treated with concurrent chemoradiation had survival rates superior to those treated with radiation alone. These two studies suggest that patients with bulky stage Ib and IIa disease should have primary treatment consisting of chemoradiation, with the chemotherapy agent being weekly cisplatin.**

Surgical Staging Before Radiation

Surgical staging procedures designed to discover positive lymph nodes have been devised. Transperitoneal exploration was initially used, but was associated with a

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16% to 33% mortality rate from radiotherapy-induced bowel complications and a 5-year survival rate of only 9% to 12% (128,129). When transperitoneal exploration was routinely employed, the subsequent radiotherapy dose to the para-aortic chain was 5,500 to 6,000 cGy, which is now known to be excessive. Intestinal morbidity was predominately a result of postsurgical adhesions entrapping the intestine in the radiotherapy field, resulting in bowel exposure to the full dose of radiation. In the absence of postsurgical adhesions, the small bowel would move in and out of the radiotherapy field and receive a lesser dose. **To avoid these complications, extraperitoneal dissection of the para-aortic nodes is now recommended, and the radiation dose should be reduced to 5,000 cGy or less (130,131). When such an approach is used, postradiotherapy bowel complications occur in fewer than 5% of patients (132,133), and the 5-year survival rate is 15% to 26% in patients with positive para-aortic nodes (17,133).** Survival appears to be related to the amount of disease in the para-aortic nodes and to the size of the primary tumor. In patients whose metastases to the para-aortic lymph nodes are microscopic and whose central tumor has not extended to the pelvic sidewall, the 5-year survival rate improves to 20% to 50% (134,135). Surgical staging techniques have improved to include laparoscopic assessment of the para-aortic and pelvic lymph nodes. Studies have demonstrated benefit from surgical staging with improved survival and changes in treatment plans in 40% of patients (131,132).

Management of Grossly Positive Para-aortic Lymph Nodes

The management of patients with macroscopic or grossly positive para-aortic lymph nodes discovered at the time of surgery or by imaging studies is controversial. It is likely that grossly positive nodes are beyond the ability of radiation therapy alone to sterilize. Therefore, to improve survival, additional therapy is required. In a representative study of the multiple reports in the literature (25), lymph node metastases were noted in 133 of 266 patients. Pelvic and para-aortic nodes were positive in 44 patients and positive para-aortic nodes were noted in only 2 patients. Five- and ten-year survival rates were similar for patients with macroscopically positive resectable nodes and microscopically positive nodes. Patients with unresectable nodal disease had a worse survival rate than those with resectable disease. All patients underwent extraperitoneal lymph node resections and subsequent radiotherapy. There was a 10% incidence of severe morbidity related to radiation use. Consistent with other reports in the literature, this study showed that **extraperitoneal debulking lymphadenectomy confers a survival advantage similar to that enjoyed by patients with micrometastatic disease without additional morbidity (25).**

Prophylactic Para-aortic Radiation Therapy

Prophylactic extended-field radiation therapy is an alternative to surgical staging of

the para-aortic lymph node chain in women with advanced cervical cancer judged to be at high risk but without radiological or clinical evidence of para-aortic lymph node involvement. This treatment strategy was evaluated in 441 patients with stage I—III disease (136). High rates of gastrointestinal toxicity were noted in the treatment group. There was no difference in disease-free survival or overall survival between the control and treated groups, although treated patients had fewer para-aortic failures. A lack of difference in survival rates in this study may be related to high local and regional failure rates, suggesting that ideal patients for prophylactic radiotherapy would be those in whom there is a high likelihood of achieving pelvic control. A survival benefit was noted in a study by the Radiation Therapy Oncology Group (137), in which 367 patients with stage Ib—IIb disease were randomized to pelvic radiotherapy versus pelvic and extended field radiotherapy. The extended field treatment arm suffered more grade 4 and 5 toxicity, confirming previous studies. Complicating the issue is another study from the Radiation Therapy Oncology Group that revealed that in locally advanced cervical cancer, pelvic radiation therapy with concurrent *cisplatin* chemotherapy was superior to extended-field radiation therapy (138).

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The appropriate role of prophylactic para-aortic radiation therapy is still under investigation.

Supraclavicular Lymph Node Biopsy

Although not standard practice, the performance of a supraclavicular lymph node biopsy has been advocated in patients with positive para-aortic lymph nodes before the initiation of extended-field irradiation as well as in patients with a central recurrence before exploration for possible exenteration. The incidence of metastatic disease in the supraclavicular lymph nodes in patients with positive para-aortic lymph nodes is 5% to 30% (139). Cytologic assessment by FNA can obviate the need for an excisional biopsy and thus should be performed if any enlarged nodes are present. If the scalene lymph nodes are found to be positive, the disease is incurable, and treatment is palliative.

Complications of Radiation Therapy

Perforation of the uterus may occur at the time of insertion of the uterine tandem. This is a problem particularly for elderly patients and those who have had a previous diagnostic conization procedure. When perforation is recognized, the tandem should be removed, and the patient should be observed for bleeding or signs of peritonitis. Survival may be decreased in patients who have had uterine perforation (140), possibly because these patients have more extensive uterine disease. Fever may occur after insertion of the uterine tandem and ovoids. Fever most often results from infection of the necrotic tumor and occurs 2 to 6 hours after insertion of the intracavitary system. If uterine perforation has been excluded by ultrasonography, intravenous broad-spectrum antibiotic coverage, usually with a cephalosporin, should be administered. If the fever does not decrease promptly or if the temperature is higher than 38.5°C, an aminoglycoside and a *Bacteroides* species—specific antibiotic should administered. If fever persists or if the patient shows signs of septic shock or peritonitis, the intracavitary system must be removed. Antibiotics are continued until the patient has recovered, and the intracavitary application is delayed for 1 to 2 weeks.

Acute Morbidity

The acute effects of radiotherapy are caused by ionizing radiation on the epithelium of

the intestine and bladder and occur after administration of 2,000 to 3,000 cGy.

Symptoms include diarrhea, abdominal cramps, nausea, frequent urination, and occasionally bleeding from the bladder or bowel mucosa. Bowel symptoms can be treated with a low-gluten, low-lactose, and low-protein diet. Antidiarrheal and antispasmodic agents may also help. Bladder symptoms may be treated with antispasmodic medication. Severe symptoms may require a week of rest from radiotherapy.

Chronic Morbidity

The chronic effects of radiotherapy result from radiation-induced vasculitis and fibrosis and are more serious than the acute effects. These complications occur several months to years after radiotherapy has been completed. The bowel and bladder fistula rate after pelvic radiation therapy for cervical cancer is 1.4% to 5.3% (57,59). Other serious toxicity (e.g., bowel bleeding, stricture, stenosis, or obstruction) occurs in 6.4% to 8.1% of patients (57,59).

Proctosigmoiditis

Bleeding from proctosigmoiditis should be treated with a low-residue diet, antidiarrheal medications, and steroid enemas. In extreme cases, a colostomy may be required to rest the bowel completely. Occasionally resection of the rectosigmoid must be performed.

Rectovaginal Fistula

Rectovaginal fistulas or rectal strictures occur in fewer than 2% of patients. The successful closure of fistulas with bulbocavernosus flaps (141) or sigmoid colon transposition (142) has been reported. Occasionally, resection with anastomosis is feasible. Diversion resulting in colostomy may be the optimal therapy in patients who have poor vascular supply to the pelvis and a history of an anastomotic leak or breakdown from prior repairs.

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Small Bowel Complications

Patients with previous abdominal surgery are more likely to have pelvic adhesions and thus sustain more radiotherapy complications in the small bowel. The terminal ileum may be particularly susceptible to chronic damage because of its relatively fixed position at the cecum. Patients with small bowel complications typically have a long history of crampy abdominal pain, intestinal rushes, and distention characteristic of partial small bowel obstruction. Often, low-grade fever and anemia accompany the symptoms.

Patients who have no evidence of disease should be treated aggressively with total parenteral nutrition, nasogastric suction, and early surgical intervention after the anemia has resolved and good nutritional status has been attained. The type of procedure performed depends on individual circumstances (143). Small bowel fistulas that occur after radiotherapy rarely close spontaneously while total parenteral nutrition is maintained. Recurrent cancer should be excluded; aggressive fluid replacement, nasogastric suction, and wound care should be instituted. Fistulography and a barium enema should be performed to exclude a combined large and small bowel fistula. The fistula-containing loop of bowel may be either resected or isolated and left *in situ*. In the latter case, the fistula will act as its own mucous fistula.

Urinary Tract

Chronic urinary tract complications occur in 1% to 5% of patients and depend on the dose of radiation to the base of the bladder. Vesicovaginal fistulas are the most common complication and usually require supravescicular urinary diversion. Occasionally, a small fistula can be repaired with either a bulbo cavernosus flap or an omental pedicle. Ureteral strictures are usually a sign of recurrent cancer, and a cytologic sample should be obtained at the site of the obstruction using FNA guided by a CT scan. If the findings are negative, the patient should undergo exploratory surgery to evaluate the presence of recurrent disease. If radiation fibrosis is the cause, ureterolysis may be possible or indwelling ureteral stents may be passed through the open urinary bladder to relieve obstruction.

Chemotherapy

Neoadjuvant Chemotherapy

Randomized trials have been initiated by the Gynecologic Oncology Group and other large centers to determine the efficacy of neoadjuvant chemotherapy. **In the era of effective chemoradiation therapy, there is no evidence that neoadjuvant chemotherapy offers superior results or a survival advantage over standard therapy.**

Chemotherapy for Advanced Disease

Chemotherapy has been studied in advanced cervical cancer with mixed results.

Single-agent chemotherapy has been the standard for advanced or recurrent disease. Active agents include *cisplatin*, *carboplatin*, *paclitaxol*, and *ifosfamide*, but response rates are only 10% to 20% with a median duration of only 4 to 6 months. More recently, a number of trials have been performed to determine whether multiagent chemotherapy is superior. The Gynecologic Oncology Group 149 studied patients with histologically confirmed, advanced stage (IVb), recurrent or persistent squamous cell cancer of the cervix and randomized these patients to one of two combination chemotherapy treatment arms. Of the 287 patients, 146 patients were randomized to the *cisplatin* and *ifosfamide* arm, and 141 patients received *cisplatin*, *ifosfamide*, and *bleomycin*. There were no differences in overall survival, progression-free survival, response rates, or overall toxicity between the two combination chemotherapy regimens (144). In another trial sponsored by the Gynecologic Oncology Group, single-agent *cisplatin* was compared to *cisplatin* plus either *dibromodulcitol* or *ifosfamide* plus *mesna*. In this trial, the combination of *cisplatin* plus *ifosfamide* had a better response rate (31% versus 18%) and median time to progression (4.6 months versus 3.2 months) compared with single agent *cisplatin*. Toxicity was notably higher in the combination regimen, and there was no overall survival advantage demonstrated (145). Recently, the Gynecologic

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Oncology Group published the results of a study comparing single-agent *cisplatin* to *cisplatin* plus *paclitaxel* in women with stage IVb squamous cell cancer of the cervix. Although the response rate (36% versus 19%) and progression-free survival (4.8 months versus 2.8 months) were greater for the combination regimen, there was only a 1-month increase in overall survival (146). Finally, the regimen of *methotrexate*, *vinblastine*, *doxorubicin*, and *cisplatin* (MVAC), which had received considerable attention because of preliminary studies suggesting high response rates, was evaluated in **Gynecologic Oncology Group protocol 179**. In this study, MVAC was compared to *cisplatin* alone, and *cisplatin* combined with *topotecan*. The MVAC arm was prematurely closed because of excessive toxicity, and the remaining *cisplatin* arms were compared. **Although the combination of *cisplatin* and *topotecan* was superior to *cisplatin* alone, the improvement in overall survival was**

only 3 months. The combination arm had a higher complete response rate, overall response rate, progression-free survival, and overall survival. Based on these results, the GOG has initiated a trial comparing *topotecan*, *paclitaxel*, *vinorelbine*, and *gemcitabine* each in combination with *cisplatin*. Overall, it appears that multiagent regimens offer an improved response rate and slightly higher overall survival but with increased toxicity.

Treatment of Cervical Cancer by Stage

Stage Ia

Until 1985, no FIGO recommendation existed concerning the size of lesion or the depth of invasion that should be considered microinvasive (stage Ia). This led to considerable confusion and controversy in the literature. Over the years, as many as 18 different definitions have been used to describe "microinvasion." In 1974, the Society of Gynecologic Oncologists recommended a definition that is now accepted by FIGO: **A microinvasive lesion is one in which neoplastic epithelium invades the stroma to a depth of less than 3 mm beneath the basement membrane and in which lymphatic or blood vascular involvement is not demonstrated.** The purpose of defining microinvasion is to identify a group of patients who are not at risk for lymph node metastases or recurrence and who therefore may be treated with less than radical therapy.

Diagnosis must be determined on the basis of a cone biopsy of the cervix. The treatment decision rests with the gynecologist and should be determined based on a review of the conization specimen with the pathologist. It is important that the pathologic condition be described in terms of (i) depth of invasion, (ii) width and breadth of the invasive area, (iii) presence or absence of lymph—vascular space invasion, and (iv) margin status. These variables are used to determine the degree of radicality of the operation and whether the regional lymph nodes should be treated (10).

Stage Ia1 \leq 3 mm Invasion

Lesions with invasion less than or equal to 3 mm have less than 1% incidence of pelvic node metastases. Within this group, it appears that the patients most at risk for nodal metastases or central pelvic recurrence are those with definitive evidence of tumor emboli in lymph vascular spaces (72,147). Therefore, patients with less than 3 mm invasion and no lymph—vascular space invasion may be treated with extrafascial hysterectomy without lymph node dissection. Therapeutic conization appears to be adequate therapy for these patients if childbearing capability is desired. Surgical margins and postconization endocervical curettage must be free of disease. If there is lymph—vascular space invasion, a type I (extrafascial) or II (modified radical) hysterectomy with pelvic lymph node dissection should be considered.

Treatment of microinvasive cervical adenocarcinoma has been complicated by a lack of agreement on approaches. Recent reports have shown that patients with stage Ia1

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cervical adenocarcinoma may be treated in a fashion similar to patients with this stage and a squamous lesion. Some providers disagree with this interpretation because of the difficulty of establishing a pathologic diagnosis of microinvasion from a glandular lesion. **Patients diagnosed with microinvasive cervical adenocarcinoma should have expert pathologic assessment before considering treatment with extrafascial hysterectomy or conization.**

Stage Ia2 3–5 mm Invasion

Lesions with invasion of >3 to 5 mm have a 3% to 8% incidence of pelvic node metastases (147,148,149); thus, pelvic node dissection is necessary for these lesions. The primary tumor may be treated with a modified radical hysterectomy (type II) or a radical trachelectomy if preservation of fertility is desired. If intermediate- or high-risk pathologic factors are identified in the surgical specimen, adjuvant radiation or chemoradiation therapy is recommended, respectively.

Stage Ib1 and Ib2 Invasive Cancer

Stage Ib lesions are subdivided into stage Ib1, which denotes lesions that are 4 cm or smaller in maximum diameter, and stage Ib2, which denotes lesions that are larger than 4 cm. These patients may be managed with either radical trachelectomy or a type III radical hysterectomy, with pelvic lymphadenectomy. Radical trachelectomy should be restricted to candidates with low-risk disease, an absence of lymph–vascular space invasion, and tumor size less than 2 cm. The para-aortic lymph node chain must be evaluated, especially if pelvic nodal disease is encountered. Adjuvant radiation therapy is recommended if intermediate-risk factors are identified postoperatively. Adjuvant chemoradiation is indicated if high-risk features are found.

Alternatively, primary chemoradiation therapy with curative intent is appropriate. A comparison of radical hysterectomy with radiation has resulted in similar survival rates for the two treatment modalities. Several studies comparing patients treated by either radical hysterectomy or radiation therapy showed similar survival rates and outcomes for both groups (81,150). However, patients treated with type III radical hysterectomy who subsequently received postoperative radiation had a higher rate of intestinal and urinary morbidity compared with patients treated with either modality alone. Therefore, some clinicians advocate using radiation and avoiding surgery in these patients because many will require adjuvant postoperative radiation.

Bulky Stage Ib2 and IIa Invasive Cancer

Patients with bulky Ib2 and IIa disease may be treated with either primary chemoradiation or radical surgery. Because many of these patients will be found to have intermediate- or high-risk factors postoperatively, strong consideration should be given to primary chemoradiation. If surgical therapy is desired, a type III radical hysterectomy with pelvic and para-aortic lymphadenectomy, followed by adjuvant chemoradiation if intermediate- or high-risk factors are present, is appropriate therapy. This option has benefits of complete surgical staging and ovarian preservation, if desired. Disadvantages of primary surgery include increased morbidity if multimodality therapy is utilized (150).

Stage IIb to IIIb Invasive Cancer

Therapy for patients with stage IIb or greater cervical cancer has traditionally been radiation therapy. Primary pelvic radiotherapy fails to control disease progression in 30% to 82% of patients with advanced cervical carcinoma (3). Two thirds of these failures occur in the pelvis (151). A variety of agents have been used in an attempt to increase the effectiveness of radiation therapy in patients with large primary tumors. **Because chemoradiation has been shown to be superior to radiation therapy alone, chemoradiation is now the preferred treatment strategy for these patients, with cisplatin the**

chemotherapy agent of choice. Nodal involvement, particularly the para-aortic lymph nodes, is the most important factor related to survival (see section on Concurrent Chemoradiation.)

Stage IVa and IVb Cancer

Although primary exenteration may be considered for patients with direct extension to the rectum or bladder, it is rarely performed. For patients with extension to the bladder, the survival rate with radiation therapy is as high as 30%, with a urinary fistula rate of only 3.8% (152). The presence of tumor in the bladder may prohibit cure with radiation therapy alone; thus, consideration must be given to removal of the bladder on completion of external beam radiation treatment. This is particularly true if the disease persists at that time and the geometry is not conducive to brachytherapy. Rectal extension is less commonly observed but may require diversion of the fecal stream before chemoradiation to avoid septic episodes from fecal contamination. In certain clinical situations, such as with patients who have stage IVa disease and present with vesicovaginal or rectovaginal fistula, urinary or rectal diversion may be performed, followed by chemoradiation. **Patients with stage IVb cervical carcinoma are candidates for chemotherapy and palliative pelvic radiation therapy. Control of symptoms with the least morbidity is of primary concern in this patient population.**

Patient Evaluation and Follow-up after Therapy

Patients who receive radiotherapy should be closely monitored to assess treatment response. Tumors may be expected to regress for up to 3 months after radiotherapy. During the pelvic examination, progressive shrinkage of the cervix and possible stenosis of the cervical os and surrounding upper vagina is expected and should be noted. During rectovaginal examination, careful palpation of the uterosacral and cardinal ligaments for nodularity is important. Cytologic assessment by FNA of suspicious areas should be performed to allow early diagnosis of persistent disease. In addition to the pelvic examination, the supraclavicular and inguinal lymph nodes should be carefully examined, and cervical or vaginal assessment should be performed every 3 months for 2 years and then every 6 months for the next 3 years. Endocervical curettage may be performed in patients with large central tumors.

Radiography of the chest may be performed yearly in patients who have advanced disease. Metastasis to the lung has been reported in 1.5% of cases. Solitary nodules are present in 25% of cases with metastasis. Resection of a solitary nodule in the absence of other persistent disease may yield some long-term survivors (153). Although intravenous pyelography (IVP) is not a part of routine postradiotherapy surveillance, it should be performed if a pelvic mass is detected or if urinary symptoms warrant evaluation. The finding of ureteral obstruction after radiotherapy in the absence of a palpable mass may indicate unresectable pelvic sidewall disease, but this finding should be confirmed, usually by FNA cytologic assessment (154).

Patients who have had radical hysterectomy and who are at high risk for recurrence may benefit from early recognition of recurrence because they might be saved with radiation therapy. In these patients, a routine CT urogram 6 to 12 months after surgery may be beneficial. After radical hysterectomy, about 80% of recurrences are detected within 2 years (155). In general, the larger the primary lesion, the shorter the median time is to recurrence (156).

Special Considerations

Cervical Cancer during Pregnancy

The incidence of invasive cervical cancer associated with pregnancy is 1.2 in 10,000 (157). A Pap test should be performed on all pregnant patients at the initial prenatal visit, and any grossly suspicious lesions should be biopsied. Diagnosis is often delayed during pregnancy because bleeding is attributed to pregnancy-related complications. **If the result of the Pap test is positive for malignant cells, and invasive cancer cannot be diagnosed using colposcopy and biopsy, a diagnostic conization procedure may be necessary.**

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Conization in the first trimester of pregnancy is associated with an abortion rate as high as 33% (158,159), as well as hemorrhagic and infectious complications. Because conization subjects the mother and fetus to complications, it should be performed only in the second trimester and only in patients with colposcopy findings consistent with cancer, biopsy-proven microinvasive cervical cancer, or strong cytologic evidence of invasive cancer. Inadequate colposcopic examination may be encountered during pregnancy in patients who have had prior ablative therapy. Close follow-up throughout pregnancy may allow the cervix to evert and develop an ectropion, allowing satisfactory colposcopy in the second or third trimester. Patients with obvious cervical carcinoma may undergo cervical biopsy and clinical staging similar to that of nonpregnant patients.

After conization, there appears to be no harm in delaying definitive treatment until fetal maturity is achieved in patients with stage Ia cervical cancer (158,160,161).

Patients with less than 3 mm of invasion and no lymphatic or vascular space involvement may be followed to term. Historically, these patients were allowed to deliver vaginally, and a hysterectomy was performed 6 weeks postpartum if further childbearing was not desired. However, in a multivariate analysis of 56 women with cervical cancer diagnosed during pregnancy and 27 women with cervical cancer diagnosed within 6 months of delivery, vaginal delivery was the most significant predictor of recurrence (162). In addition, most recurrences after vaginal delivery involved distant sites. The ideal delivery method for these patients is not known definitively; however, strong consideration should be given to performing a cesarean birth in women with cervical cancer of any stage (162). If vaginal delivery is chosen, close inspection of the episiotomy site is required during follow-up because of rare reports of metastatic cervical cancer at these locations (163).

Patients with 3 to 5 mm of invasion and those with lymph—vascular space invasion may also be followed to term or delivered early after establishment of fetal pulmonary maturity (158,161). They may be delivered by cesarean birth, followed immediately by modified radical hysterectomy and pelvic lymphadenectomy. **Patients with more than 5 mm invasion should be treated as having frankly invasive carcinoma of the cervix.** Treatment depends on the gestational age of the pregnancy and the wishes of the patient. Modern neonatal care affords a 75% survival rate for infants delivered at 28 weeks of gestation and 90% for those delivered at 32 weeks of gestation. Fetal pulmonary maturity can be determined by amniocentesis, and prompt treatment can be instituted when pulmonary maturity is documented. Although timing is controversial, it is probably unwise to delay therapy for longer than 4 weeks (160,161). The recommended treatment is classic cesarean delivery followed by radical hysterectomy with pelvic lymph node dissection. There should be a thorough discussion of the risks and options with both parents before any treatment is undertaken.

Patients with stage II—IV cervical cancer should be treated with radiotherapy. If the fetus is viable, it is delivered by classic cesarean birth, and therapy is begun postoperatively. If the pregnancy is in the first trimester, external radiation therapy can be started with the expectation that spontaneous abortion will occur before the delivery of

4,000 cGy. In the second trimester, a delay of therapy may be entertained to improve the chances of fetal survival. If the patient wishes to delay therapy, it is important to ensure fetal pulmonary maturity before delivery is undertaken.

The clinical stage is the most important prognostic factor for cervical cancer during pregnancy. Overall survival is slightly better because an increased proportion of these patients have stage I disease. For patients with advanced disease, there is evidence that pregnancy impairs the prognosis (158,161). The diagnosis of cancer in the postpartum period is associated with a more advanced clinical stage and a corresponding decrease in survival (162).

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Cancer of the Cervical Stump

Cancer of the cervical stump was more common many decades ago when supracervical hysterectomy was popular; however, as this operation has gained new popularity, this situation may again become more common. Early-stage disease is treated surgically, with very little change in technique from that used when the uterus is intact (164). Radical parametrectomy with upper vaginectomy and pelvic lymphadenectomy is the standard procedure. Advanced-stage disease may present a therapeutic problem for the radiotherapist if the length of the cervical canal is less than 2 cm. This length is necessary to allow satisfactory placement of the uterine tandem. If the uterine tandem cannot be placed, radiation therapy can be completed with vaginal ovoids or with an external treatment plan in which lateral ports are used to augment the standard anterior and posterior ports. Such a technique will reduce the dosage to the bowel and bladder and thus reduce the incidence of complications.

Pelvic Mass

The origin of a pelvic mass must be clarified before treatment is initiated. A CT urogram can exclude a pelvic kidney, and a barium enema helps to identify diverticular disease or carcinoma of the colon. An abdominal x-ray film may show calcifications typically associated with benign ovarian teratomas or uterine leiomyomas. Pelvic ultrasonography differentiates between solid and cystic masses and indicates uterine or adnexal origin. Solid masses of uterine origin are most often leiomyomas and generally do not need further investigation.

Pyometra and Hematometra

An enlarged fluid-filled uterine cavity may be a pyometra or a hematometra. The hematometra can be drained by dilation of the cervical canal and will not interfere with treatment. The pyometra also should be drained, and the patient should be given antibiotics to cover *Bacteroides* species, anaerobic *Staphylococcus* and *Streptococcus* species, and aerobic coliform bacterial infection. Placement of a large mushroom catheter through the cervix has been advocated, but the catheter itself may become obstructed, leading to further occlusion of the drainage. Repeated dilation of the cervix with aspiration of pus every 2 to 3 days is more effective.

If the disease is stage I, a radical hysterectomy and pelvic lymphadenectomy may be performed. However, a pyometra is usually found in patients with advanced disease, and thus radiotherapy is required. External-beam therapy can begin when the pyometra has healed. Patients often have a significant amount of pus in the uterus or a tubo-ovarian abscess without signs of infection; therefore, a normal temperature and a normal white blood cell count do not necessarily exclude infection. Repeat physical examination or pelvic ultrasonography is necessary to ensure adequate drainage.

Cervical Carcinoma after Extrafascial Hysterectomy

When invasive cervical cancer is found after simple hysterectomy, further treatment is predicated on the extent of disease. Microinvasive disease in patients at low risk for lymph node metastasis does not require further treatment. Invasive disease may be treated with radiotherapy or reoperation involving a pelvic node dissection and radical excision of parametrial tissue, cardinal ligaments, and the vaginal stump (165).

Reoperation

Reoperation is indicated particularly for a young patient who has a small lesion and in whom preservation of ovarian function is desirable. It is not indicated for patients who have positive margins or obvious residual disease (165). Survival rates after radical reoperation are similar to those after radical hysterectomy for stage I disease.

Radiation Therapy

Survival after radiotherapy depends on the volume of disease, the status of the surgical margins, and the length of delay from surgery to radiotherapy.

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Patients with microscopic disease have a 95% to 100% 5-year survival rate; the 5-year survival rate is 82% to 84% in those with macroscopic disease and free margins, 38% to 87% in those with microscopically positive margins, and 20% to 47% in those with obvious residual cancer (166,167,168). A delay in treatment of more than 6 months is associated with a 20% survival rate (168).

Acute Hemorrhage

Occasionally, a large lesion can produce life-threatening hemorrhage. A biopsy of the lesion should be performed to verify neoplasia, and a vaginal pack soaked in Monsel's solution (*ferric subsulfate*) should be packed tightly against the cervix. After proper evaluation, **external radiation therapy can be started with the expectation that control of bleeding may require 8 to 10 daily treatments at 180 to 200 cGy/day.** Broad-spectrum antibiotics should be used to reduce the incidence of infection. If the patient becomes febrile, the pack should be removed. Rapid replacement of the pack may be necessary, and a fresh pack should be immediately available. This approach to management of hemorrhage in patients previously untreated is preferable to exploration and vascular ligation.

Occasionally, vascular embolization under fluoroscopic control may be required in severe cases, and this procedure may obviate a laparotomy. However, vascular occlusion ultimately may lead to decreased blood flow and oxygenation of the tumor, compromising the effectiveness of subsequent radiotherapy.

Ureteral Obstruction

Treatment of bilateral ureteral obstruction and uremia in previously untreated patients should be determined on an individual basis. Transvesical or percutaneous ureteral catheters should be placed in patients with no evidence of distant disease, and radiotherapy with curative intent should be instituted. Patients with metastatic disease beyond curative treatment fields should be presented with the options of ureteral stenting, palliative radiotherapy, and chemotherapy. With aggressive management, a median survival rate of 17 months may be achieved for these patients (169).

Barrel-shaped Cervix

The expansion of the upper endocervix and lower uterine segment by tumor has been referred to as a **barrel-shaped cervix**. **Patients with tumors larger than 6 cm in diameter have a 17.5% central failure rate when treated with radiotherapy alone because the tumor at the periphery of the lower uterine segment is too far from the standard intracavitary source to receive an adequate tumoricidal dose** (170). Attempts have been made to overcome this problem radiotherapeutically by means of interstitial implants into the tumor with a perineal template, but high central failure rates have also been reported with this technique (171).

One approach is to use a combination of radiotherapy and surgery for treatment of patients with a barrel-shaped cervix. An extrafascial hysterectomy is performed 2 to 3 months after the completion of radiation therapy in an effort to resect a small, centrally persistent tumor. The dose of external radiotherapy is reduced to 4,000 cGy, and a single intracavitary treatment is given, which is followed by an extrafascial hysterectomy (172,173). This method appears to result in a lower rate of central failure (2%), although it is not clear that the overall survival rate is improved. **There is disagreement concerning the need for extrafascial hysterectomy**, and the Gynecologic Oncology Group is undertaking a randomized study to compare adjuvant hysterectomy with radiotherapy alone in patients who have no evidence of occult metastases in the para-aortic nodes (see Stage Ib and IIa discussion).

The narrow upper vagina of older patients may preclude the use of an intracavitary source of radiation. Such patients must receive their entire course of therapy from external sources, leading to a higher central failure rate and more significant bowel and bladder morbidity. If stage I disease is present in such a patient, a radical hysterectomy with pelvic

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lymphadenectomy is preferable if the patient's medical condition allows such an approach. There may be a role for IMRT in the management of such tumors.

Recurrent Cervical Cancer

Treatment of recurrent cervical cancer depends on the mode of primary therapy and the site of recurrence. Patients who have been treated initially with surgery should be considered for radiation therapy, and those who have had radiation therapy should be considered for surgical treatment. Chemotherapy is palliative only and is reserved for patients who are not considered curable by either surgery or radiation therapy.

Radiotherapy for recurrence after surgery consists primarily of external treatment. Vaginal ovoids also may be placed in patients with isolated vaginal cuff recurrences. Patients with a regional recurrence may require interstitial implantation with a Syed type of template in addition to external therapy. A 25% survival rate can be expected in patients treated with radiation for a postsurgical recurrence (155).

Radiation Retreatment

Retreatment of recurrent pelvic disease by means of radiotherapy with curative intent is confined to patients who have had suboptimal or incomplete primary therapy. This may allow the radiotherapist to deliver curative doses of radiation to the tumor. The proximity of the bladder and rectum to the cancer and the relative sensitivity of these organs to radiation injury are the major deterrents to retreatment with radiation. The insertion of multiple interstitial radiation sources into locally recurrent cancer through a perineal template may

help overcome these dosimetric considerations (165,174). The fistula rates are high, however, and the consequences must be considered seriously before interstitial therapy is initiated. In general, for patients considered curable with interstitial implant therapy, pelvic exenteration is a better treatment choice. Palliative radiotherapy can be given to patients with localized metastatic lesions that are deemed incurable. Painful bony metastases, central nervous system lesions, and severe urologic or vena caval obstructions are specific indications.

Surgical Therapy

Surgical therapy for postirradiation recurrence is limited to patients with central pelvic disease. A few carefully selected patients with small-volume disease limited to the cervix may be treated with an extrafascial or radical hysterectomy. However, the difficulty of assessing tumor volume and the 30% to 50% rate of serious urinary complications in these previously irradiated patients have led most gynecologic oncologists to recommend pelvic exenteration as a last chance for cure (175,176).

Exenteration

There are three types of exenterative procedures: (i) an anterior exenteration (removal of the bladder, vagina, cervix, and uterus), (ii) a posterior exenteration (removal of the rectum, vagina, cervix, and uterus), and (iii) a total exenteration (removal of both bladder and rectum with the vagina, cervix, and uterus [Fig. 34.9]). A total exenteration that includes a large perineal phase includes the entire rectum and leaves the patient with a permanent colostomy as well as a urinary conduit (**infralevator**). In selected patients, a total exenteration may take place above the levator muscle (**supralevator**), leaving a rectal stump that may be anastomosed to the sigmoid, thus avoiding a permanent colostomy.

Preoperative Evaluation and Patient Selection

It is imperative to search for metastatic disease before undergoing an exenteration. The presence of metastatic disease in this setting is considered a contraindication to exenterative procedures. Physical examination includes careful palpation of the peripheral lymph nodes with FNA

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cytologic sampling of any nodes that appear suspicious. A random biopsy of nonsuspicious supraclavicular lymph nodes has been advocated by some clinicians but is not routinely practiced (139,177). A CT scan of the lung can detect disease missed on routine radiographic examination of the chest. Abdominal and pelvic CT scans are helpful in the detection of liver metastases and enlarged para-aortic nodes. Cytologic study of any abnormality should be undertaken with CT-guided FNA. If a positive cytologic diagnosis is obtained, it will obviate the need for exploratory laparotomy.

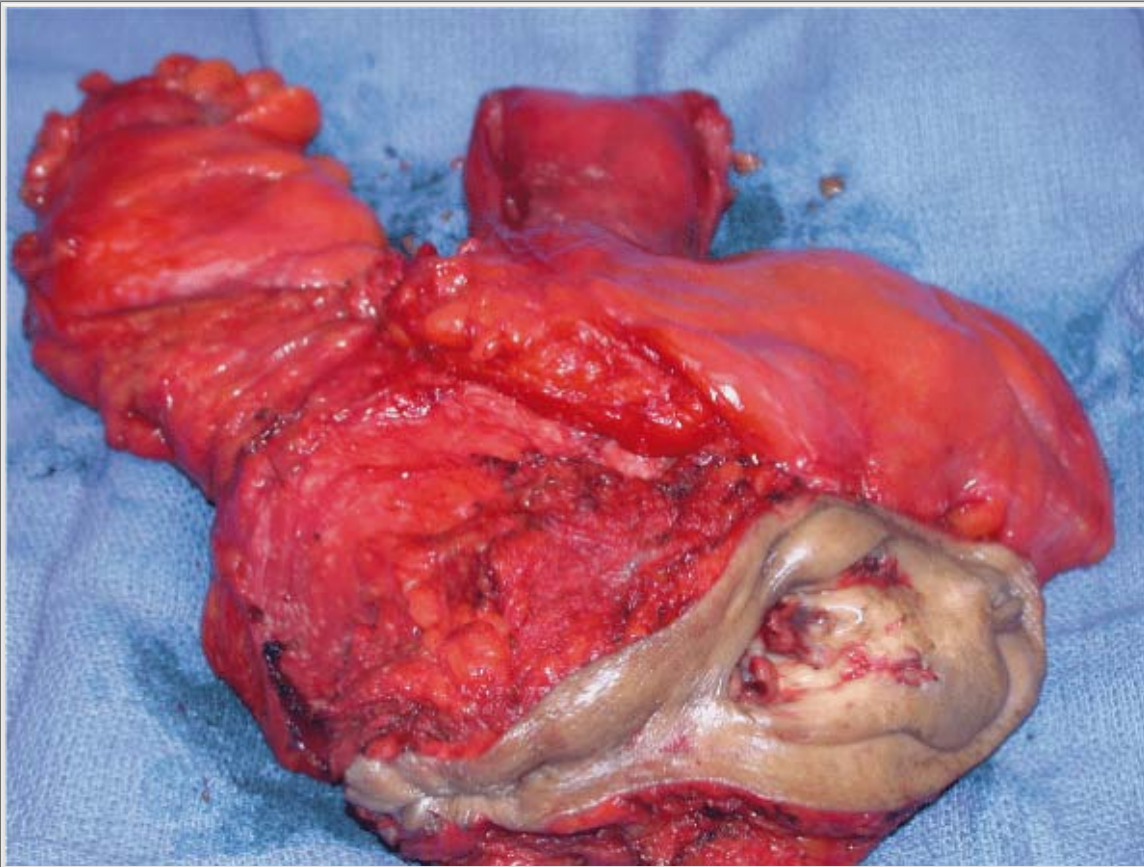


Figure 34.9 Pelvic exenteration.

Extension of the tumor to the pelvic sidewall is a contraindication to exenteration; however, this may be difficult for even the most experienced examiner to determine because of radiation fibrosis. If any question of resectability arises, exploratory laparotomy and parametrial biopsies should be offered (178,179,180,181). **The clinical triad of unilateral leg edema, sciatic pain, and ureteral obstruction is nearly always pathognomonic of unresectable disease on the pelvic sidewall.** Preoperatively, the patient should be prepared for a major operation. Total parenteral nutrition may be necessary to place the patient in an anabolic state for optimal healing. A bowel preparation, preoperative antibiotic administration, and prophylaxis for deep venous thrombosis with low-dose heparin or pneumatic calf compression should be undertaken (182). Surgical mortality increases with age, and the operation should rarely be considered in a patient who is older than 70 years. Other medical illnesses should be taken into account. When life expectancy is limited, exenterative surgery is unwise.

Anterior Exenteration

Candidates for anterior exenteration are those in whom the disease is limited to the cervix and anterior portion of the upper vagina. Proctoscopic examination should be performed because a positive finding would mandate a total exenteration. However, a negative proctoscopic examination finding does not exclude disease in the rectal muscularis, and findings at laparotomy still must be considered. Generally, the presence of disease in the posterior vaginal mucosa directly over the rectum mandates removal of the underlying rectum.

Posterior Exenteration

A posterior exenteration is rarely performed for recurrent cervical cancer. It is indicated, however, for the patient with an isolated posterior vaginal recurrence in which dissection of the ureters through the cardinal ligaments will not be necessary.

Total Exenteration

Total exenteration with a large perineal phase is indicated when the disease extends to the lower part of the vagina (see Fig. 34.9). Because distal vaginal lymphatics may empty into the nodal basins of the inguinal region, these nodes should be carefully evaluated preoperatively. A supralelevator total exenteration with low rectal anastomosis is indicated in the patient whose disease is confined to the upper vagina and cervix (183,184). Samples from margins of the rectal edge should be obtained for frozen-section evaluation because occult metastases to the muscularis may occur.

The development of techniques to establish continent urinary diversion has helped improve a woman's physical appearance after exenteration (185,186,187).

When both a rectal anastomosis and a continent diversion are performed, the patient will not have a permanent external appliance. Associated psychological trauma in such cases may be avoided. **Every effort should be made to create a neovagina simultaneously with the exenteration** (188). This procedure helps in the reconstruction of the pelvic floor after extirpation of the pelvic viscera. Regardless whether a neovagina is constructed, it is desirable to mobilize the omentum on the left gastroepiploic artery to create a new pelvic floor.

Surgical mortality from exenterative procedures has steadily decreased to an acceptable level of less than 10%. Common causes of postoperative death are sepsis, pulmonary thromboembolism, and hemorrhage. Fistulas of the gastrointestinal and genitourinary tract are serious surgical complications, with a 30% to 40% mortality rate despite attempts at surgical repair. The risk for fistula formation has decreased because nonirradiated segments of bowel have been used for formation of the urinary conduit (182). **The 5-year survival rate is 33% to 60% for patients undergoing anterior exenteration and 20% to 46% for those undergoing total exenteration** (178,179,180,181,182,183,184,185,186,187,188). Survival rates are worse for patients with recurrent disease (larger than 3 cm), invasion into the bladder, positive pelvic lymph nodes, and recurrence diagnosed within 1 year after radiotherapy (181). The 5-year survival rate of patients with positive pelvic lymph nodes is less than 5%; thus, the performance of an extensive lymphadenectomy in the irradiated field is not warranted. Discontinuation of the procedure is advisable if any nodes are positive for metastatic cancer. Patients who have any disease in the peritoneal cavity have no chance of survival.

Laterally Extended Endopelvic Resection

Locally recurrent cervical cancer in a previously irradiated field is associated with a dismal prognosis. Exenterative therapy has traditionally been reserved for the highly select patient with centrally recurrent disease, a selection criteria that excludes most patients with recurrence. Recently, a new technique called **laterally extended endopelvic resection (LEER)** procedure has been described, which offers a new surgical treatment option for patients with recurrent disease involving the pelvic sidewall. The LEER procedure involves extending the lateral resection plane of the traditional pelvic exenteration to include resection of the internal iliac vessels; the endopelvic portion of the obturator internus muscle; and the coccygeus, iliococcygeus, and pubococcygeus muscles. Extension of the surgical plane allows for resection of lateral tumors with a negative margin. Experience with it is limited (189).

Chemotherapy for Recurrent Cervical Cancer

Recurrent cervical cancer is not considered curable with chemotherapy. The delivery of chemotherapy to recurrent tumor in a prior radiated field may be compromised because of altered blood supply caused by radiation. **Topotecan and cisplatin has been reported to have response rates of 15% to 20%, with a median duration of 6 to 9 months (190).**

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Many other agents have shown activity against cervical cancer and may be used in attempt to help control symptoms. **Several clinical trials with various drugs (e.g., paclitaxel, topotecan, cisplatin, and carboplatin) have shown response rates of up to 45%. Most responses are partial (191), and complete responses are unusual and are generally limited to patients with chest metastases,** in whom the dose of drug delivered to the disease is stronger than that delivered to the fibrotic postirradiated pelvis (192).

Palliative Therapy

Palliative therapy for patients with incurable disease consists of radiation or chemotherapy or both. **Palliative radiation therapy is intended to relieve symptoms of pain or bleeding associated with advanced disease and may be administered as either external beam therapy (teletherapy) or brachytherapy.** Special care should be given to previously irradiated sites because additional radiation therapy may be associated with unacceptable morbidity. Single or multiagent palliative chemotherapy may also be used with variable response rates. Symptomatic recurrent disease within previously irradiated fields may not respond well to palliative chemotherapy.

Vaginal Carcinoma

Primary vaginal cancer is a relatively uncommon tumor, representing only 1% to 2% of malignant neoplasms of the female genital tract (193,194). The incidence of invasive vaginal cancer is 0.42 per 100,000 women, and it has remained relatively unchanged since the 1980s (195). Primary vaginal cancer should be differentiated from cancers metastatic to the vagina, which constitute the majority of vaginal cancers (80% to 90%) (196).

Staging

The FIGO staging of vaginal cancer dictates that a tumor extending to the vagina from the cervix be regarded as a cancer of the cervix, whereas a tumor involving both the vulva and the vagina should be classified as a cancer of the vulva.

The FIGO staging for vaginal carcinoma is shown in Table 34.6. **Staging is performed by clinical examination** and, if indicated, cystoscopy, proctoscopy, and chest and skeletal radiography. Information derived from lymphangiography, CT, MRI, or PET cannot be used to change the FIGO stage; however, it can be used for planning treatment. Unfortunately, 75% of patients present with stage II–IV disease, complicating the treatment and subsequent cure rates (197,198,199).

Table 34.6 FIGO Staging of Vaginal Cancer

Stage 0	Carcinoma <i>in situ</i> , intraepithelial carcinoma.
Stage I	The carcinoma is limited to the vaginal wall.
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall.
Stage III	The carcinoma has extended to the pelvic wall.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum.
	IVa Spread of the growth to adjacent organs.
	IVb Spread to distant organs.
FIGO, International Federation of Gynecology and Obstetrics.	

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Surgical staging and resection of enlarged lymph nodes may be indicated in selected patients. FIGO staging does not include a category for microinvasive disease. Because vaginal cancer is rare, and treatment is generally by radiotherapy, there is very little information concerning the spread of disease in relation to depth of invasion, lymph—vascular space invasion, and size of the lesion.

Etiology

The cause of squamous cell carcinoma of the vagina is unknown. The association of cervical cancer with HPV suggests that vaginal cancer may have a similar association (200).

Human papillomavirus has been recovered from 80% of precursor lesions and 60% of squamous cell cancers of the vagina (53,54). In addition, as many as 30% of women with vaginal cancer have a history of cervical cancer treated within the previous 5 years (201,202,203). As with cervical cancer, there appears to be a premalignant phase called **vaginal intraepithelial neoplasia (VAIN)** (see Chapter 17). **The exact incidence of progression to invasive vaginal cancer from VAIN is not known;** however, there are documented cases of invasive disease occurring despite adequate treatment of VAIN (204,205).

By convention, any new vaginal carcinoma developing at least 5 years after cervical cancer should be considered a new primary lesion. There are three possible mechanisms for the occurrence of vaginal cancer after cervical neoplasia:

- Residual disease in the vaginal epithelium after treatment of the cervical neoplasia
- New primary disease arising in a patient with increased susceptibility to lower genital tract carcinogenesis (the role of HPV in this setting is suspected)
- Increased susceptibility to carcinogenesis caused by radiation therapy

Screening

Routine screening of all patients for vaginal cancer is inappropriate. For women who have had a cervical or vulvar neoplasm, the Pap test is an important part of routine follow-up with each physician visit, as these patients are at an increased lifetime risk for developing

vaginal cancer. It is recommended that Pap test surveillance for vaginal cancer be performed yearly after the patient has completed surveillance for cancer of the cervix or vulva. **For women who have had a hysterectomy for benign disease and have no antecedent history of CIN 2–3, performance of Pap testing is unnecessary. If the patient has a history of cervical dysplasia or cervical cancer, yearly screening is recommended.**

When adjusted for age and prior cervical disease, the incidence of vaginal cancer is not increased in women who have had hysterectomy for benign disease (206). Because primary vaginal tumors tend to be multicentric, the entire vaginal mucosa should be considered at risk. Therefore, in addition to screening cytology, careful bimanual examinations of the entire vagina and vulva is recommended for women at high risk.

Symptoms

Painless vaginal bleeding and discharge are the most common symptoms of vaginal cancer. With more advanced tumors, urinary retention, bladder spasm, hematuria, and frequency of urination may occur. Tumors developing on the posterior vaginal wall may produce rectal symptoms, such as tenesmus, constipation, or blood in the stool.

Diagnosis

The diagnostic workup includes a complete history and physical examination, careful speculum examination and palpation of the vagina, and bimanual pelvic and rectal

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examinations. **It is important to rotate the speculum to obtain a careful view of the entire vagina because posterior wall lesions frequently occur and may be overlooked.**

In early squamous cell lesions, the diagnosis is often suggested by an abnormal Pap test result; however, this is not true for clear cell adenocarcinomas, which are characterized by submucosal growth. In these cases, the diagnosis is suggested by cytologic findings in only 33% of cases. Visually suspicious areas in the vagina should be evaluated with a targeted biopsy using the same instruments as those used for cervical biopsies. Careful palpation of the vagina may be helpful in detecting submucosal irregularities. **The most common site of vaginal cancer is in the upper one third of the vagina on the posterior wall.**

The developing tumor may be missed during initial inspection because of obscured visualization caused by the blades of the speculum (207). Colposcopy is valuable in evaluating patients with abnormal Pap test results, unexplained vaginal bleeding, or ulcerated erythematous patches in the upper vagina. A colposcopically targeted biopsy may not allow a definitive diagnosis, and a partial vaginectomy may be necessary to determine invasion. Occult invasive carcinoma may be detected by such an excision, particularly in patients who have a history of prior hysterectomy in whom the vaginal vault closure may bury some of the vaginal epithelium at risk for cancer (208).

Pathology

Cancer of the vagina spreads most often by direct extension into the pelvic soft tissues and adjacent organs. Metastases to the pelvic and para-aortic lymph nodes may occur in advanced disease. Lesions in the lower one third of the vagina may spread directly to the inguinal femoral lymph nodes as well as the pelvic nodes (209). Hematogenous dissemination to the lungs, liver, or bone may occur as a late phenomenon.

Squamous cell carcinomas are the most common form of vaginal cancer, occurring in 80% to 90% of cases. These tumors most commonly occur in the upper one third, posterior wall of the vagina. The mean age of patients with squamous cell cancer is 60 years

(210,211). Malignant melanoma is the second most common cancer of the vagina, accounting for 2.8% to 5% of all vaginal neoplasms (212,213,214). Other histologic subtypes include adenocarcinoma and sarcoma.

Primary adenocarcinoma of the vagina is rare, constituting 9% of primary tumors of the vagina. The most common adenocarcinoma of the vagina is metastatic, originating from the colon, endometrium, ovary, or, rarely, pancreas and stomach.

In general, adenocarcinomas affect a younger population of women, regardless of whether they were exposed to *diethylstilbestrol (DES) in utero* (215). Adenocarcinomas may arise in wolffian rest elements, periurethral glands, and foci of endometriosis (216). In women exposed to *DES in utero*, adenocarcinoma may develop in vaginal adenosis.

Diethylstilbestrol was used in the United States from 1940 until 1971 to maintain high-risk pregnancies in women with a history of spontaneous abortions. In 1970, seven young women were reported with clear cell adenocarcinoma of the vagina (Fig. 34.10); later, an association between this cancer and maternal ingestion of *DES* during pregnancy was identified (217). Subsequently, more than 500 cases of clear cell cancer of the vagina and cervix have been reported to the Registry for Research on Hormonal Transplacental Carcinogenesis.

The estimated risk for developing clear cell adenocarcinoma for an exposed offspring is 1 in 1,000 or less. The mean age of diagnosis is 19 years (218). Clear cell adenocarcinoma in women with a history of *in utero* exposure to *DES* typically presents in the exocervix or anterior, upper one third of the vagina. These tumors vary greatly in size and are most frequently exophytic and superficially invasive. Stage is the most important prognostic factor. Other statistically significant factors include a tubulocystic growth pattern,

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size less than 3 cm², and less than 3 mm of stromal invasion. Because the use of *DES* in pregnant women was discontinued in 1971, most of these tumors probably have been discovered. It is uncertain, however, what will happen to this cohort of women as they move into their fifth, sixth, and seventh decades of life. Continued surveillance of these women is indicated.

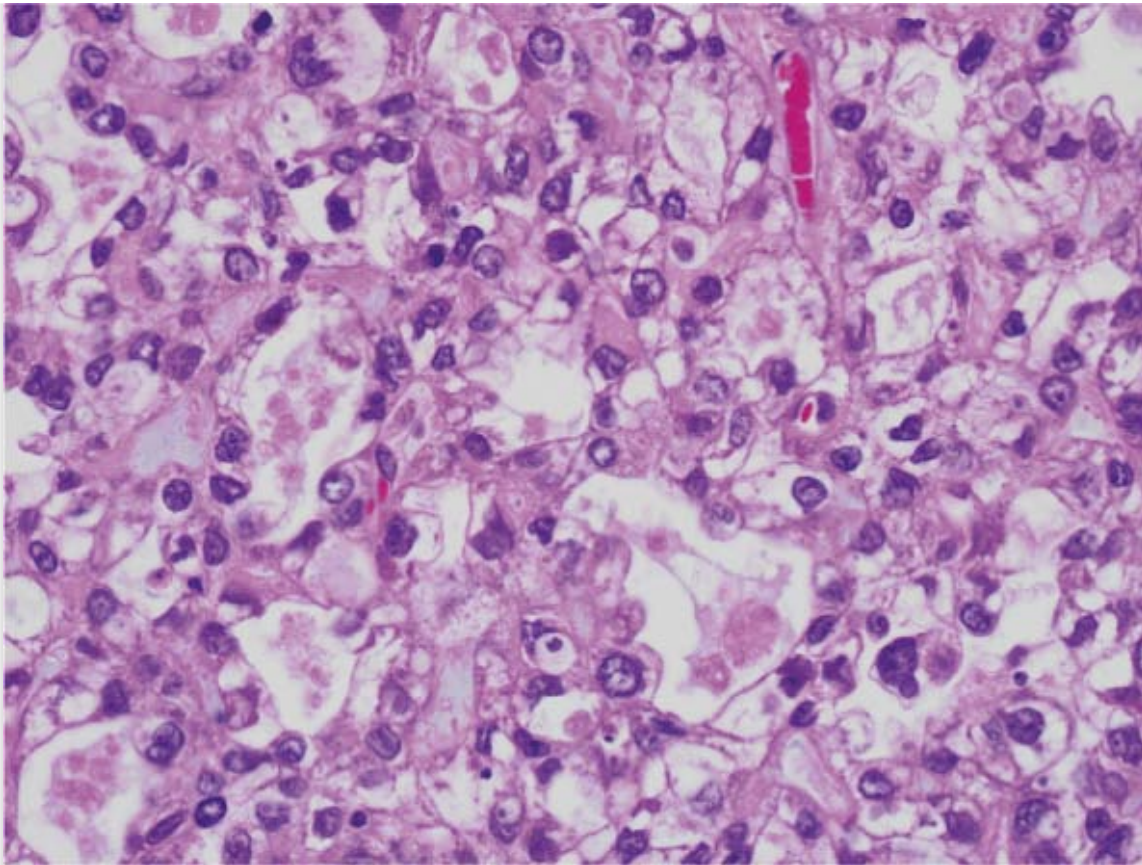


Figure 34.10 Vaginal clear cell carcinoma. Note the formation of tubules with hobnail cells lining the lumen. These cells are characterized by nuclear protrusion into the apical cytoplasm.

Ninety-seven percent of cases of vaginal clear cell adenocarcinoma are associated with adenosis. Adenosis is characterized by the presence of persistent müllerian-type glandular epithelium. Although adenosis is the most common histologic abnormality in women exposed to *DES in utero*, adenosis can also be found in women without a history of exposure. Adenosis typically appears as red, grapelike clusters in the vagina.

Malignant melanoma of the vagina is rare and extremely lethal, occurring most often in white women. The average age of these patients is 58 years (219). Most lesions are deeply invasive, corresponding to a Clark level IV when compared with the staging for vulvar melanomas. The most common location of these tumors is in the lower one third of the vagina (220). Melanomas have a wide variety of size, color, and growth patterns (218,221). Radical excision (vaginectomy, hysterectomy, and pelvic lymphadenectomy) has been the mainstay of treatment. The goal of treatment is to avoid local (vaginal) recurrence, which is the most common site of recurrence (219,220). The need to dissect regional lymph nodes is uncertain. Because the disease is deeply invasive, hematogenous spread is the most common lethal recurrence. There is no difference in overall survival of patients with local as opposed to radical excision (219). The survival rate is approximately 10% at 5 years.

The most common benign and malignant mesenchymal tumors of the vagina in adult women are smooth muscle tumors (222). Vaginal sarcomas are usually fibrosarcomas or

leiomyosarcomas and are extremely rare. Radical local excision, followed by adjuvant chemotherapy or radiation therapy, is the indicated treatment.

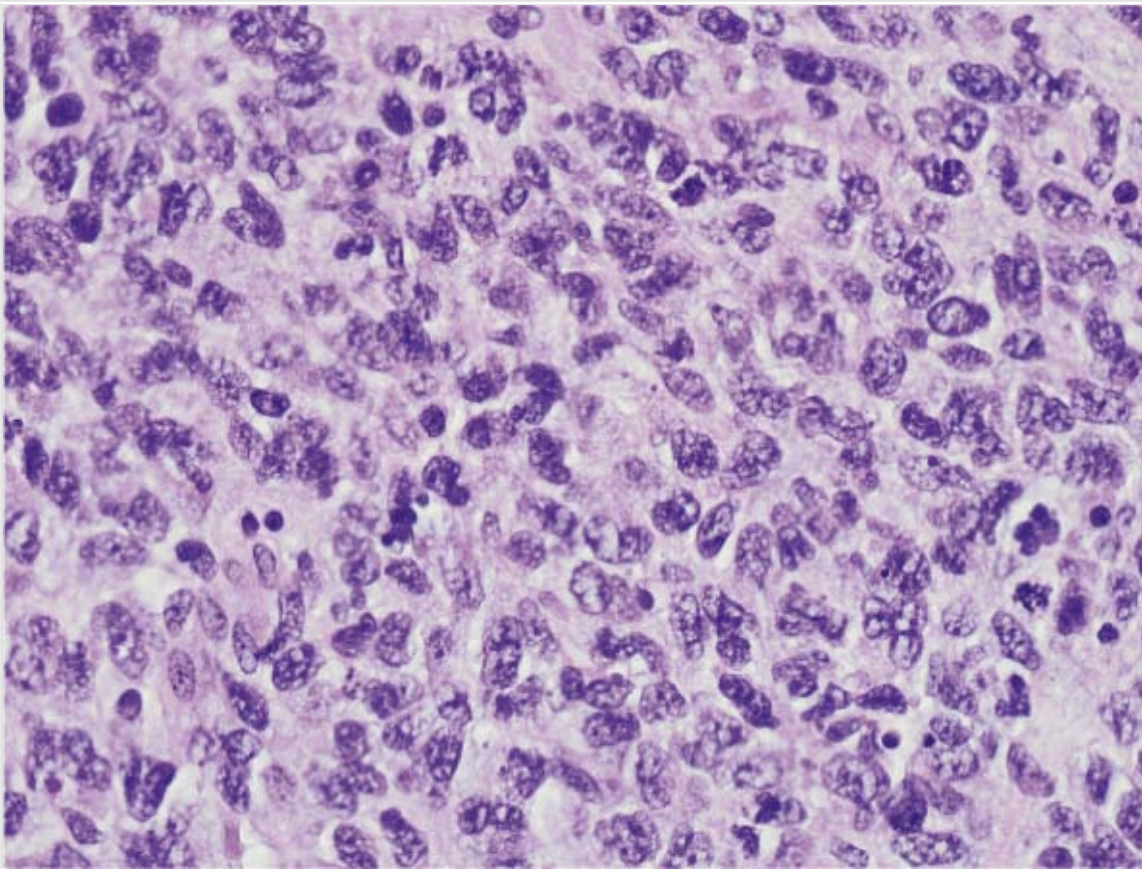


Figure 34.11 Embryonal rhabdomyosarcoma of the vagina (botryoid sarcoma). This lesion consists of primitive mesenchymal cells and rhabdomyoblasts, which have abundant eosinophilic cytoplasm. With further differentiation, cross striations may become evident.

The most common malignant mesenchymal tumor of the vagina in children and infants is botryoid rhabdomyosarcoma (Fig. 34.11). Botryoid sarcoma is usually found in the vagina during infancy and early childhood, in the cervix during the reproductive years, and in the corpus uteri during postmenopausal years. Preoperative chemotherapy with *vincristine*, *actinomycin D*, and *cyclophosphamide*, followed by conservative surgery or radiation, has led to improved survival.

Treatment

Treatment selection is based on the clinical examination, CT scan results, chest radiography results, age, and condition of the patient. Most tumors are treated by radiation therapy. Surgery is limited to highly selective cases.

Women with stage I disease involving the upper posterior vagina may be treated by radical vaginectomy and pelvic lymphadenectomy. If the uterus is *in situ*, it is removed as a radical hysterectomy specimen. When margins are clear and lymph nodes are negative, no additional therapy is necessary. Patients with stage IV disease with either rectovaginal or vesicovaginal fistula may be candidates for primary pelvic exenteration with pelvic and para-aortic node dissection (218). Low rectal anastomosis, continent urinary diversion, and vaginal reconstruction are indicated and are more successful in these nonirradiated patients than in patients who receive prior radiation therapy (188).

Women with central pelvic recurrence after radiation therapy are candidates for pelvic exenteration similar to that used for cervical cancer. Surgical staging with

resection of enlarged lymph nodes followed by radiation therapy may improve the control of pelvic disease.

Radiation therapy is the treatment of choice for all patients except those described previously. Small superficial lesions may be treated with intracavitary radiation alone (218). Larger, thicker lesions should be treated first with external teletherapy to decrease tumor volume and to treat the regional pelvic nodes, followed by intracavitary and interstitial therapy to deliver a high dose to the primary tumor (211,219). If the uterus is intact and the lesion involves the upper vagina, an intrauterine tandem and ovoids can be used. If the uterus has been previously removed, a vaginal cylinder may be used for superficial irradiation. When brachytherapy is used, high- and low-dose rate techniques have been described. If the lesion is more than 0.5 cm thick, interstitial radiation techniques can improve the dose distribution to the primary tumor. Surgical exploration or laparoscopy at the time of insertion of Syed interstitial implants defines more precisely the placement of the needles and ensures that needles do not pass into adherent loops of bowel. Extended-field radiation may be used for vaginal cancer in a manner similar to its use for cervical carcinoma, although there is no experience reported with the use of this technique in the treatment of vaginal cancer. Likewise, there is no reported experience with combination chemoradiation treatment. However, **concurrent use of 5-FU and cisplatin has been highly successful in anal and cervical cancer and thus should be considered for treatment of vaginal cancer.**

Sequelae

The proximity of the rectum, bladder, and urethra leads to a major complication rate of 10% to 15% for both surgery and radiation treatment. For large tumors, the risk of bladder or bowel fistula is significant. Radiation cystitis and proctitis are common, as are rectal strictures or ulcerations. Radiation necrosis of the vagina occasionally occurs, requiring débridement, and often leads to fistula formation. Vaginal fibrosis, stenosis, and stricture are common after radiation therapy. **Use of vaginal dilators and resumption of regular sexual relations should be encouraged, along with the use of topical estrogen to maintain adequate vaginal function.**

Survival

The overall 5-year survival rate for patients with vaginal cancer is 42% (Table 34.7). Even for patients with stage I disease, the 5-year survival rate is less than 70%, which is 15% lower than that for comparable stages of cervical or vulvar cancer (220,221,222,223,224). Most recurrences are in the pelvis, either from enlarged regional nodes or from large central tumors. Radiation techniques, including interstitial implants with Syed applicator and combination chemoradiation, are the mainstay of therapy. Careful evaluation of patients who receive radiation therapy to detect central recurrence may allow some

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patients to be saved by pelvic exenteration. Because of the rarity of vaginal cancer, these patients should be treated in a center that is familiar with the complexity of treatment and modalities of therapy.

Table 34.7 Primary Vaginal Carcinoma: 5-year Survival

Stage	No. of Patients	No. Surviving 5 Years	Percentage
I	172	118	68.6
II	236	108	45.8
III	203	62	30.5
IV	114	20	17.5
Total	725	308	42.5

Data compiled from **Benedet et al.**, 1983 (198); **Rubin et al.**, 1985 (200); **Kucera et al.**, 1985 (221); **Houghton and Iversen**, 1982 (222); **Eddy et al.**, 1991 (223); and **Pride et al.**, 1979 (224).

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35

Ovarian and Fallopian Tube Cancer

Jonathan S. Berek

Sathima Natarajan



- **The peak incidence of invasive epithelial ovarian cancer is at 56 to 60 years of age. About 30% of ovarian neoplasms in postmenopausal women are malignant, whereas only about 7% of ovarian epithelial tumors in premenopausal patients are frankly malignant. The average age of patients with borderline tumors is approximately 46 years.**
- **Ovarian cancer has been associated with low parity and infertility. Because parity is inversely related to the risk of ovarian cancer, having at least one child**

is protective of the disease, with a risk reduction of 0.3 to 0.4.

- Oral contraceptive use reduces the risk of epithelial ovarian cancer. Women who use oral contraceptives for 5 or more years reduce their relative risk to 0.5 (i.e., there is a 50% reduction in the likelihood of development of ovarian cancer).
- Given the false-positive results for both CA125 and transvaginal ultrasonography, particularly in premenopausal women, these tests are not cost-effective and should not be used routinely to screen for ovarian cancer.
- Most epithelial ovarian cancer is sporadic, with familial or hereditary patterns accounting for 5% to 10% of all malignancies. Hereditary ovarian cancers in general occur in women approximately 10 years younger than those with nonhereditary tumors.
- Most hereditary ovarian cancer is associated with germline mutations in the *BRCA1* gene; a small proportion of inherited disease is associated with mutations in the gene *BRCA2*. The mutations are inherited in an autosomal dominant fashion, and therefore a full pedigree analysis (i.e., both maternal and paternal sides of the family) must be carefully evaluated. The value of prophylactic salpingo-oophorectomy in these patients has been documented.
- The importance of thorough surgical staging cannot be overemphasized, because subsequent treatment will be determined by the stage of disease. Patients with advanced-stage disease should undergo "debulking" or cytoreductive surgery to remove as much of the tumor and its metastases as possible, if the patient is medically stable. The performance of a debulking operation as early as possible in the course of the patient's treatment should be considered the standard of care.
- Combination chemotherapy with *carboplatin* and *paclitaxel* is the treatment of choice for patients with high-risk, low-stage disease. For advanced-stage epithelial ovarian cancer, the choice of intravenous versus intraperitoneal platinum and taxane chemotherapy should be individualized.
- In the first two decades of life, almost 70% of ovarian tumors are of germ

cell origin, and one third of these are malignant. In contrast to the relatively slow-growing epithelial ovarian tumors, germ cell malignancies grow rapidly.

- **The most common types of malignant germ cell tumors are dysgerminomas, immature teratomas, and endodermal sinus tumors. Preservation of fertility should be standard in most patients. The most effective chemotherapy is *bleomycin, etoposide, and cisplatin* (BEP) combination.**
- **Stromal tumors include granulosa cell tumors, which are low-grade malignancies. In premenopausal women, they can be treated conservatively. Adjuvant chemotherapy is of unproven value.**
- **Metastatic tumors to the ovaries are most frequently from the breast and gastrointestinal tract.**
- **Fallopian tube carcinomas are treated the same as ovarian cancer, with staging, cytoreductive surgery, and platinum and taxane chemotherapy.**

Of all the gynecologic cancers, ovarian malignancies represent the greatest clinical challenge. Epithelial cancers are the most common ovarian malignancies, and because they are usually asymptomatic until they have metastasized, patients have advanced disease at diagnosis in more than two thirds of the cases. Ovarian cancer represents a major surgical challenge, requires intensive and often complex therapies, and is extremely demanding of the patient's psychological and physical energy. It has the highest fatality-to-case ratio of all the gynecologic malignancies. There are more than 20,000 new cases annually in the United States, and more than 15,000 women can be expected to succumb to their illness (1). Ovarian cancer is the seventh most common cancer in women in the United States, accounting for 3% of all malignancies and 6% of deaths from cancer in women, and almost one third of invasive malignancies of the female genital organs. Ovarian cancer is the fifth most common cause of death from malignancy in women. **A woman's risk at birth of having ovarian cancer sometime in her life is 1% to 1.5%, and that of dying from ovarian cancer almost 0.5%** (2).

Epithelial Ovarian Cancer

Approximately 90% of ovarian cancers are derived from tissues that come from the coelomic epithelium or mesothelium (2). The cells are a product of the primitive mesoderm, which can undergo metaplasia. A classification of the histologic types of epithelial tumors of the ovary is presented in Table 35.1. Neoplastic transformation can occur when the

cells are genetically predisposed to oncogenesis or exposed to an oncogenic agent or both (3).

Table 35.1 Epithelial Ovarian Tumors	
<i>Histologic Type</i>	<i>Cellular Type</i>
<i>I. Serous</i>	<i>Endosalpingeal</i>
A. Benign	
B. Borderline	
C. Malignant	
<i>II. Mucinous</i>	<i>Endocervical</i>
A. Benign	
B. Borderline	
C. Malignant	
<i>III. Endometrioid</i>	<i>Endometrial</i>
A. Benign	
B. Borderline	
C. Malignant	
<i>IV. Clear-cell "mesonephroid"</i>	<i>Mullerian</i>
A. Benign	
B. Borderline	
C. Malignant	
<i>V. Brenner</i>	<i>Transitional</i>
A. Benign	
B. Borderline (proliferating)	
C. Malignant	
<i>VI. Mixed epithelial</i>	<i>Mixed</i>
A. Benign	
B. Borderline	
C. Malignant	
<i>VII. Undifferentiated</i>	<i>Anaplastic</i>
<i>VIII. Unclassified</i>	<i>Mesothelioma, etc.</i>
From Seroy SF, Scully RE, Sobin LH. <i>International histological classification of tumours no. 9. Histological typing of ovarian tumors.</i> Geneva, Switzerland: World Health Organization, 1973, with permission.	

Pathology

Invasive Cancer

Seventy-five percent of epithelial cancers are of the serous histologic type. Less common types are mucinous (20%), endometrioid (2%), clear cell, Brenner, and undifferentiated carcinomas; each of the last three types represents less than 1% of epithelial lesions (2). Each tumor type has a histologic pattern that reproduces the mucosal features of a section of the lower genital tract (3). For example, the serous or papillary pattern has an appearance similar to that of the glandular epithelial lining and fallopian

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tube. Mucinous tumors contain cells that resemble the endocervical glands, and the endometrioid tumors resemble the endometrium.

Borderline Tumors

An important group of tumors to distinguish is the *tumor of low malignant potential*, also called the *borderline tumor*. Borderline tumors are lesions that tend to remain confined to the ovary for long periods, occur predominantly in premenopausal women, and are associated with a very good prognosis (2,3,4,5,6,7,8). They are encountered most frequently in women between the ages of 30 and 50 years, whereas invasive carcinomas occur more often in women between the ages of 50 and 70 years (2).

Although uncommon, metastatic implants may occur with borderline tumors. Such implants have been divided into *noninvasive* and *invasive* forms. The latter group has a higher likelihood of developing into progressive, proliferative disease in the peritoneal cavity, which can lead to intestinal obstruction and death (2,6).

The criteria for the diagnosis of borderline tumors (Fig. 35.1) are as follows (7):

- **Epithelial hyperplasia in the form of pseudostratification, tufting, cribriform, and micropapillary architecture**
- **Nuclear atypia and increased mitotic activity**
- **Detached cell clusters**
- **Absence of destructive stromal invasion (i.e., without tissue destruction)**

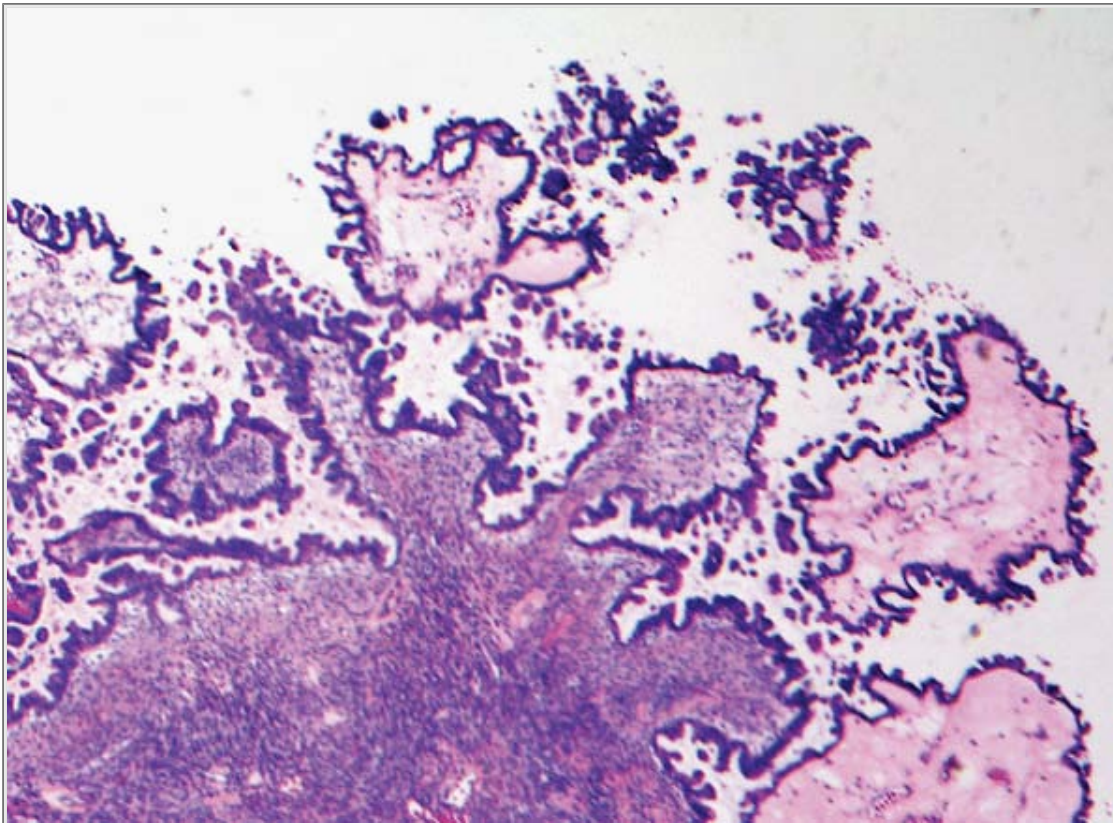


Figure 35.1 Borderline malignant serous tumor of the ovary. Complex papillary fronds are lined with pseudostratified columnar cells. The epithelium and the stroma are clearly separated by a basement membrane, indicating no stromal invasion.

It should be emphasized that about 20% to 25% of borderline tumors spread beyond the ovary. **The diagnosis of borderline tumor versus malignant ovarian tumor must be based on the histologic features of the primary tumor (7).**

Classification of Epithelial Ovarian Tumors

Serous Tumors

Serous tumors develop by invagination of the surface ovarian epithelium and are so classified because they secrete serous fluid (as do tubal secretory cells).

Psammoma bodies, more correctly foci of foreign material, frequently are associated with these invaginations and may be a response to irritative agents that produce adhesion formation

and the entrapment of the surface epithelium. In the wall of the mesothelial invaginations, papillary ingrowths are common, representing the early stages of development of a papillary serous cystadenoma. There are many variations in the proliferation of these mesothelial inclusions. Several foci may be lined with flattened inactive epithelium; in adjacent cavities, papillary excrescences are present, often resulting from local irritants (2).

Borderline Serous Tumors

Approximately 10% of all ovarian serous tumors fall into the category of a tumor of low malignant potential or borderline tumor, and 50% occur before the age of 40 years.

As many as 10% of women with ovarian serous borderline tumors have extraovarian implants, and some will eventually die of the disease (9). Although multiple foci of disease have been documented in the abdominal cavity with secondary deposits in the pelvis, omentum, and adjacent tissues, including lymph nodes, metastases outside the abdominal cavity are rare. Death can occur as the result of intestinal obstruction (10,11,12).

The implants are divided histologically into *invasive* and *noninvasive implants* (6,10). In the noninvasive implants, papillary proliferations of atypical cells involve the peritoneal surface and form smooth invaginations (6). The invasive implants resemble well-differentiated serous carcinoma and are characterized by atypical cells forming irregular glands with sharp borders. Bell et al. (6) have reported that only three of 50 women with noninvasive implants died, whereas four of six women with invasive implants died. In the series of McCaughey et al., two of 13 patients with noninvasive implants and all five patients with invasive implants died (9). Others have noted no differences in prognosis (10,11).

Rare examples of borderline malignant serous tumors with foci of microinvasion have been reported by Bell and Scully (12). Most patients are young, International Federation of Gynecology and Obstetrics (FIGO) stage I, and sometimes pregnant. Only one of 30 such patients died of disease, and she had stage III disease.

Malignant Serous Carcinomas

In malignant serous tumors, stromal invasion is present (2). The grade of tumor should be identified. In well-differentiated serous adenocarcinomas, papillary and glandular structures predominate (Fig. 35.2); poorly differentiated neoplasms are characterized by solid sheets of cells, nuclear pleomorphism, and high mitotic activity; and moderately differentiated carcinomas are intermediate between these two lesions. Laminated, calcified psammoma bodies are found in 80% of serous carcinomas. ***Serous psammocarcinoma is a rare variant of serous carcinoma characterized by massive psammoma body formation and low-grade cytological features.*** At least 75% of the epithelial nests are associated with psammoma body formation. Patients with serous psammocarcinoma have a protracted clinical course and a relatively favorable prognosis; their clinical course more closely resembles that of serous borderline tumor than serous carcinoma.

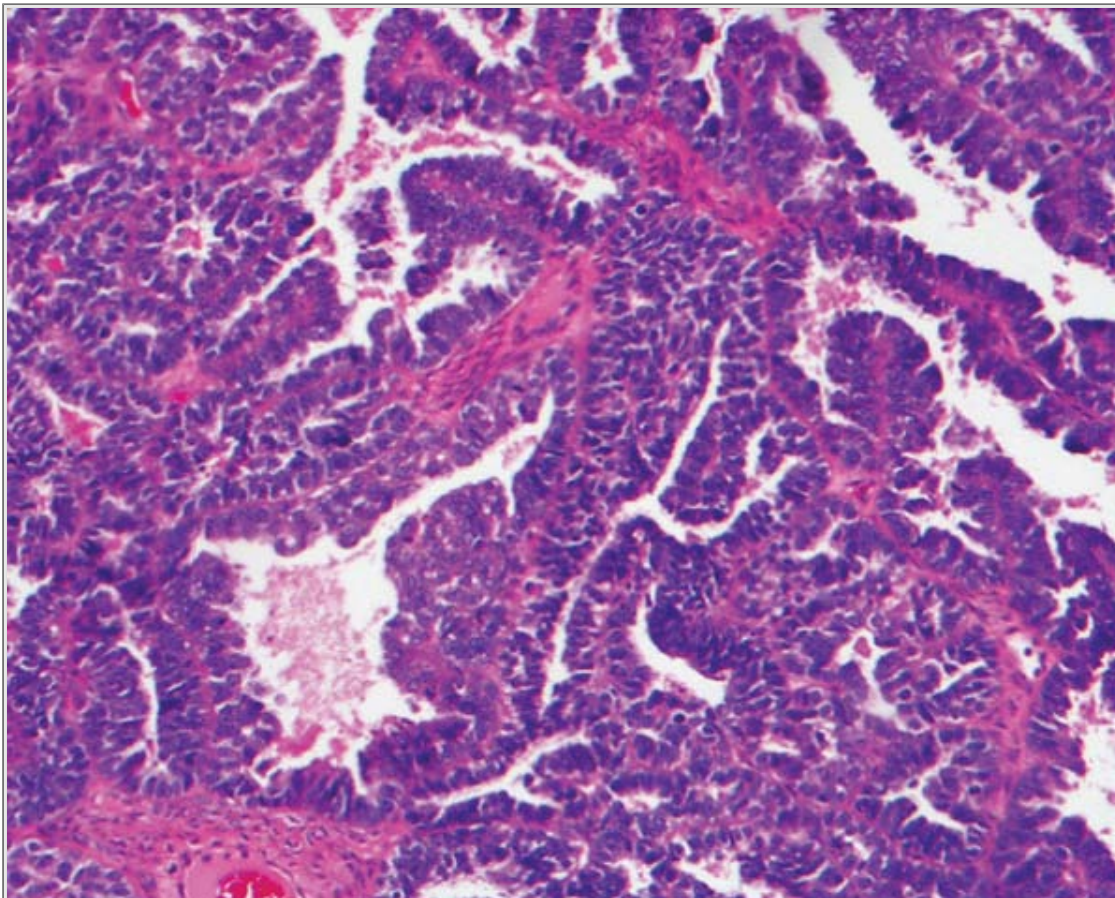


Figure 35.2 Well-differentiated serous papillary adenocarcinoma of the ovary. Clusters and papillae of malignant cells are in direct contact with fibrous stroma indicative of stromal invasion.

Mucinous Tumors

These cystic ovarian tumors have loculi lined with mucin-secreting epithelium. The lining epithelial cells contain intracytoplasmic mucin and resemble those of endocervix, gastric pylorus, or intestina. **They represent about 8% to 10% of epithelial ovarian tumors.** They may reach enormous size, filling the entire abdominal cavity (2).

Borderline Mucinous Tumors

The mucinous tumor of low malignant potential is often a diagnosis difficult to make. Although it is common to find a rather uniform pattern from section to section in the serous borderline

tumor, this is not true in the mucinous tumors. **Frequently, well-differentiated mucinous epithelium may be seen immediately adjacent to a poorly differentiated focus. Therefore, it is important to take multiple sections from many areas in the mucinous tumor to identify the most malignant alteration.**

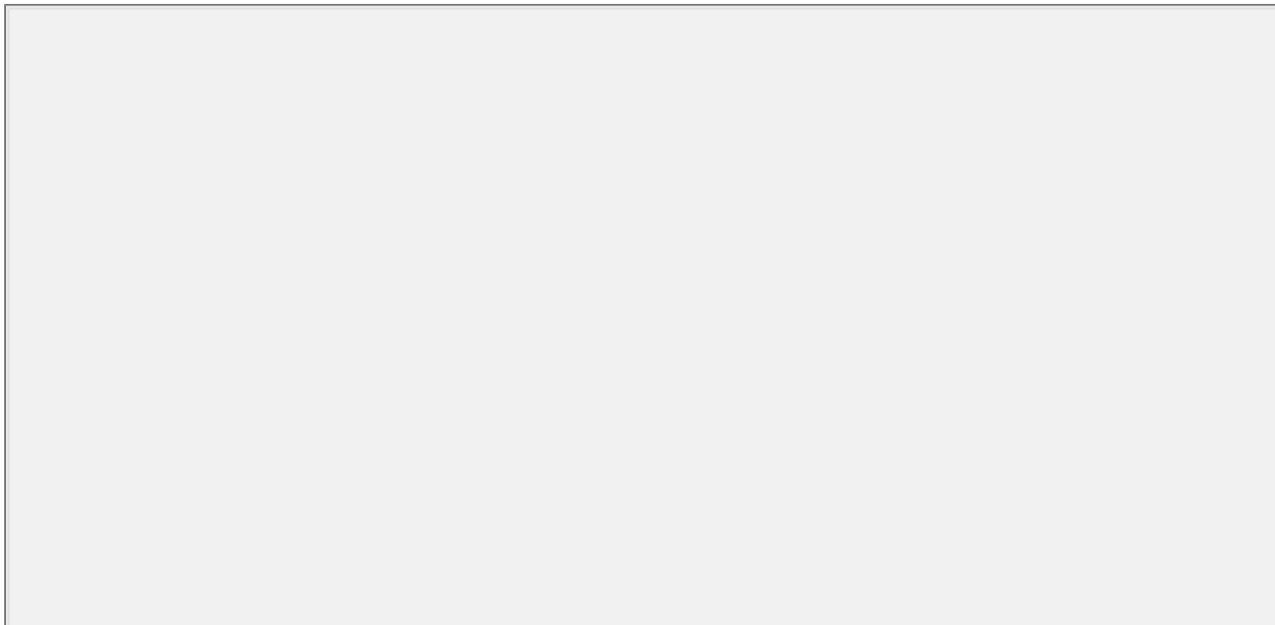
Malignant Mucinous Carcinomas

Bilateral tumors occur in 8% to 10% of cases. The mucinous lesions are intraovarian in 95% to 98% of cases (Fig. 35.3). **Because most ovarian mucinous carcinomas contain intestinal-type cells, they cannot be distinguished from metastatic carcinoma of the gastrointestinal tract on the basis of histology alone.** Primary ovarian neoplasms rarely metastasize to the mucosa of the bowel, although they commonly involve the serosa, whereas gastrointestinal lesions frequently involve the ovary by direct extension of vascular lymphatic spread.

Pseudomyxoma Peritonei

Pseudomyxoma peritonei is a clinical term used to describe the finding of abundant mucoid or gelatinous material in the pelvis and abdominal cavity surrounded by fibrous tissue. It is **most commonly secondary to a well-differentiated**

appendiceal carcinoma or other gastrointestinal primary, and less commonly, a mucocele of the appendix.



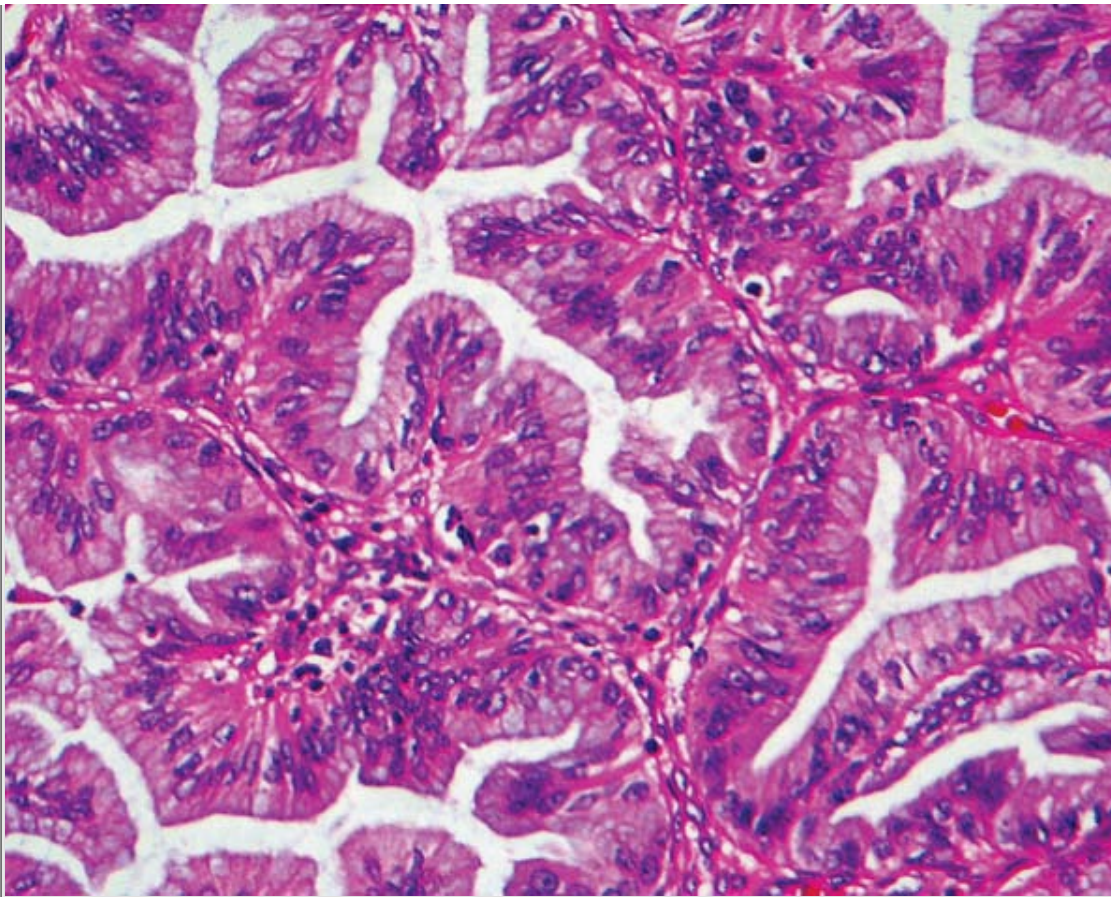


Figure 35.3 Mucinous adenocarcinoma of the ovary. Irregular glandular spaces are lined with a layer of tall columnar cells with abundant mucinous cytoplasm, resembling endocervical cells. The nuclei are mildly atypical.

Endometrioid Tumors

Endometrioid lesions constitute 6% to 8% of epithelial tumors. Endometrioid neoplasia includes all the benign demonstrations of endometriosis. In 1925, Sampson (13) suggested that certain cases of adenocarcinoma of the ovary probably arose in areas of endometriosis. The adenocarcinomas are similar to those seen in the uterine corpus. The malignant potential of endometriosis is very low, although a transition from benign to malignant epithelium may be demonstrated (Fig. 35.4).

Borderline Endometrioid Tumors

The endometrioid tumor of low malignant potential has a wide morphologic

spectrum. Tumors may resemble an endometrial polyp or complex endometrial hyperplasia with glandular crowding. When there are back-to-back glands with no intervening stroma, the tumor is classified as a well-differentiated endometrioid carcinoma. Some borderline endometrioid tumors have a prominent fibromatous component. In such cases, the word *adenofibroma* is used.

Malignant Endometrioid Carcinomas

Endometrioid tumors are characterized by an adenomatous pattern with all the potential variations of epithelia found in the uterus.

Multifocal Disease

The *endometrial* or endometrioid tumors afford the greatest opportunity to evaluate multifocal disease. **Endometrioid carcinoma of the ovary is associated in 15% to 20% of the cases with carcinoma of the endometrium. Identification of multifocal disease is important, because patients with disease metastatic from the**

uterus to the ovaries have a 30% to 40% 5-year survival, whereas those with synchronous multifocal disease have a 75% to 80% 5-year survival (14). When the histologic appearance of endometrial and ovarian tumors is different, the two tumors most likely represent two separate primary lesions. When they appear similar, the endometrial tumor can be considered a separate primary tumor if it is well differentiated and only superficially invasive.

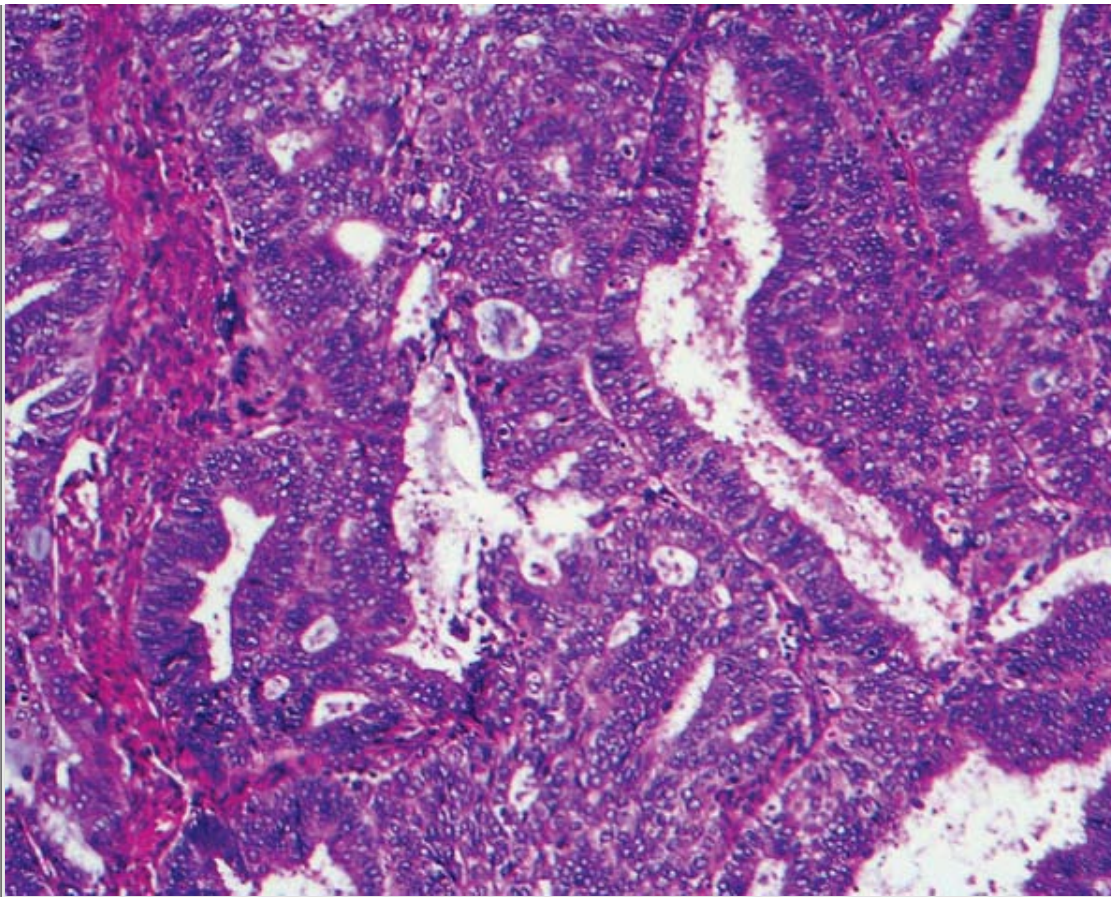


Figure 35.4 Endometrioid cancer. Round to tubular glands lined by stratified columnar cells with confluent growth pattern.

Clear Cell Carcinomas

Several basic histologic patterns are present in the clear cell adenocarcinoma (i.e., tubulocystic, papillary, reticular, and solid). The tumors are made up of clear and hobnail cells that project their nuclei to the apical cytoplasm. The tall clear cells have abundant clear or vacuolated cytoplasm, hyperchromatic irregular nuclei, and nucleoli of various sizes (Fig. 35.5). **Focal areas of endometriosis and endometrioid carcinoma sometimes occur.** The clear cell carcinoma seen in the ovary is histologically identical to that seen in the uterus or vagina of the young patient who has been exposed to diethylstilbestrol (DES) *in utero*. Nuclei of clear cell carcinoma range from grade 1 to grade 3, but pure grade 1 tumors are extremely rare. **Almost invariably high-grade (grade 3) nuclei are identified. Hence, clear cell carcinoma is not graded.**

Brenner Tumors

Borderline Brenner Tumors

Borderline, or proliferating, Brenner tumors have been described. In such cases, the epithelium does not invade the stroma. Some investigators subclassify those tumors that resemble low-grade papillary transitional cell carcinoma of the urinary bladder as proliferating tumors and those with a higher grade of transitional cell carcinoma *in situ* as borderline malignant Brenner tumors (15). Complete surgical removal usually results in cure.

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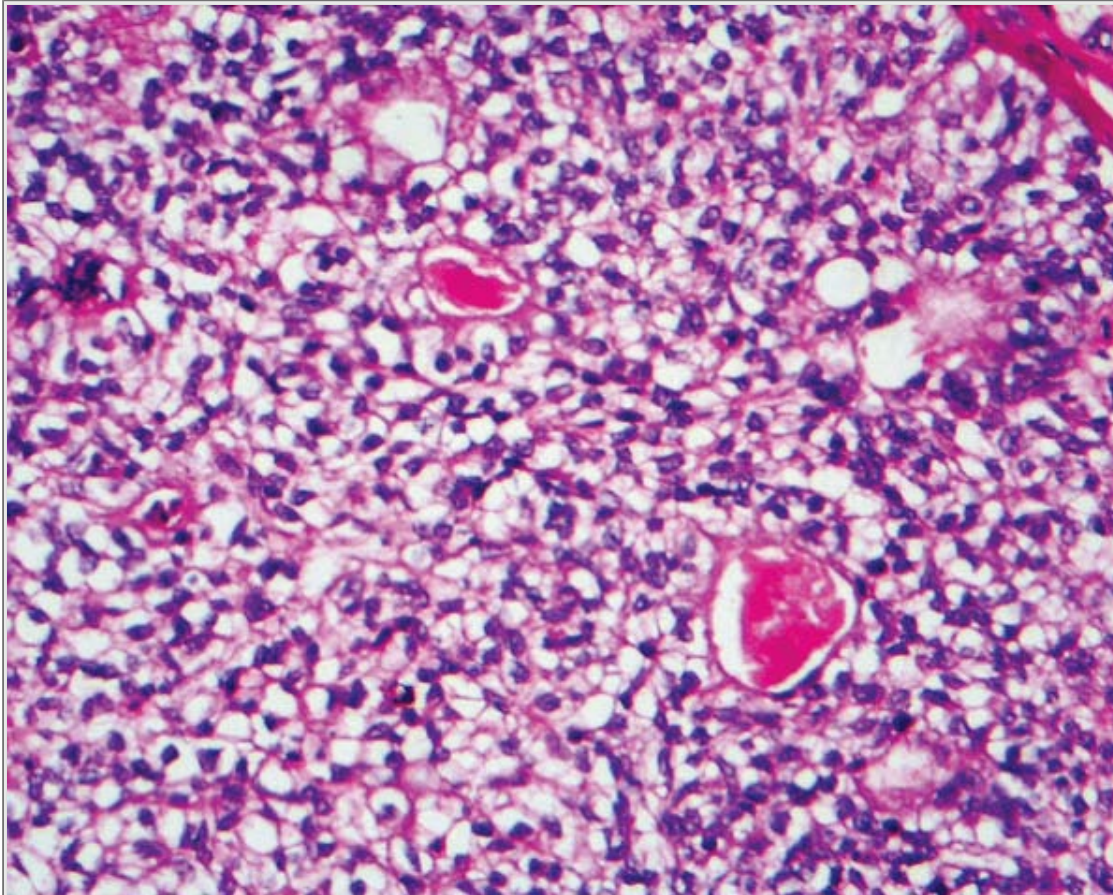


Figure 35.5 Clear cell mesonephroid carcinoma of the ovary. Note the solid variant of clear cell carcinoma with sheets of cells that have clear cytoplasm ("hobnail" cells).

These are rare and are defined as **benign Brenner tumors coexisting with invasive transitional cells or another type of carcinoma**. In malignant Brenner tumors there is stromal invasion associated with a benign or borderline Brenner tumor component.

Transitional Cell Tumors

The designation *transitional cell tumor* refers to a **primary ovarian carcinoma resembling transitional cell carcinoma of the urinary bladder without a recognizable Brenner tumor**. An important finding is that those ovarian carcinomas that contain more than 50% of transitional cell carcinoma are more sensitive to chemotherapy and have a more favorable prognosis than other poorly differentiated ovarian carcinomas of comparable stage (16,17). Transitional cell tumors differ from malignant Brenner tumors in that they are more frequently diagnosed in an advanced stage and, therefore, are associated with a poorer survival rate (18).

Small cell carcinoma occurs mainly in young women, who may have symptoms of hypercalcemia. Immunohistochemical stains are helpful to differentiate this tumor from a lymphoma, leukemia, or sarcoma.

Peritoneal Carcinomas

Primary peritoneal tumors are histologically indistinguishable from primary ovarian serous tumors. In the case of *borderline serous peritoneal tumors* and *serous peritoneal carcinomas*, the ovaries are normal or minimally involved, and the tumors affect predominantly the uterosacral ligaments, pelvic peritoneum, or omentum. The overall prognosis for borderline serous peritoneal tumors is excellent and comparable to that of ovarian borderline serous tumors (19,20,21). In the review of 38 cases of peritoneal borderline serous

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tumors from the literature, 32 women had no persistent disease, four were well after resection of recurrence, one developed an invasive serous carcinoma, and one died from the effects of the tumor (19).

Peritoneal serous carcinomas have the appearance of a moderately to poorly differentiated serous ovarian carcinoma. Primary peritoneal endometrioid carcinoma is less common.

The primary malignant transformation of the peritoneum has been called primary peritoneal carcinoma or primary peritoneal papillary serous carcinoma. Peritoneal carcinoma simulates ovarian cancer clinically. In patients for whom exploratory surgery is performed, there may be microscopic or small macroscopic cancer on the surface of the ovary and extensive disease in the upper abdomen, particularly in the

omentum. **This phenomenon can thus produce a condition in which so-called ovarian cancer can arise in a patient whose ovaries were surgically removed many years earlier** (22).

Mesotheliomas

Peritoneal malignant mesotheliomas fall into the following four categories (2,23):

(i) fibrosarcomatous, (ii) tubulopapillary (papillary-alveolar), (iii) carcinomatous, and (iv) mixed. These lesions appear as multiple intraperitoneal masses and can develop after hysterectomy and bilateral salpingo-oophorectomy for benign disease.

Malignant mesotheliomas should be distinguished from ovarian tumor implants and primary peritoneal müllerian neoplasms.

Clinical Features

More than 80% of epithelial ovarian cancers are found in postmenopausal women (Fig. 35.6).

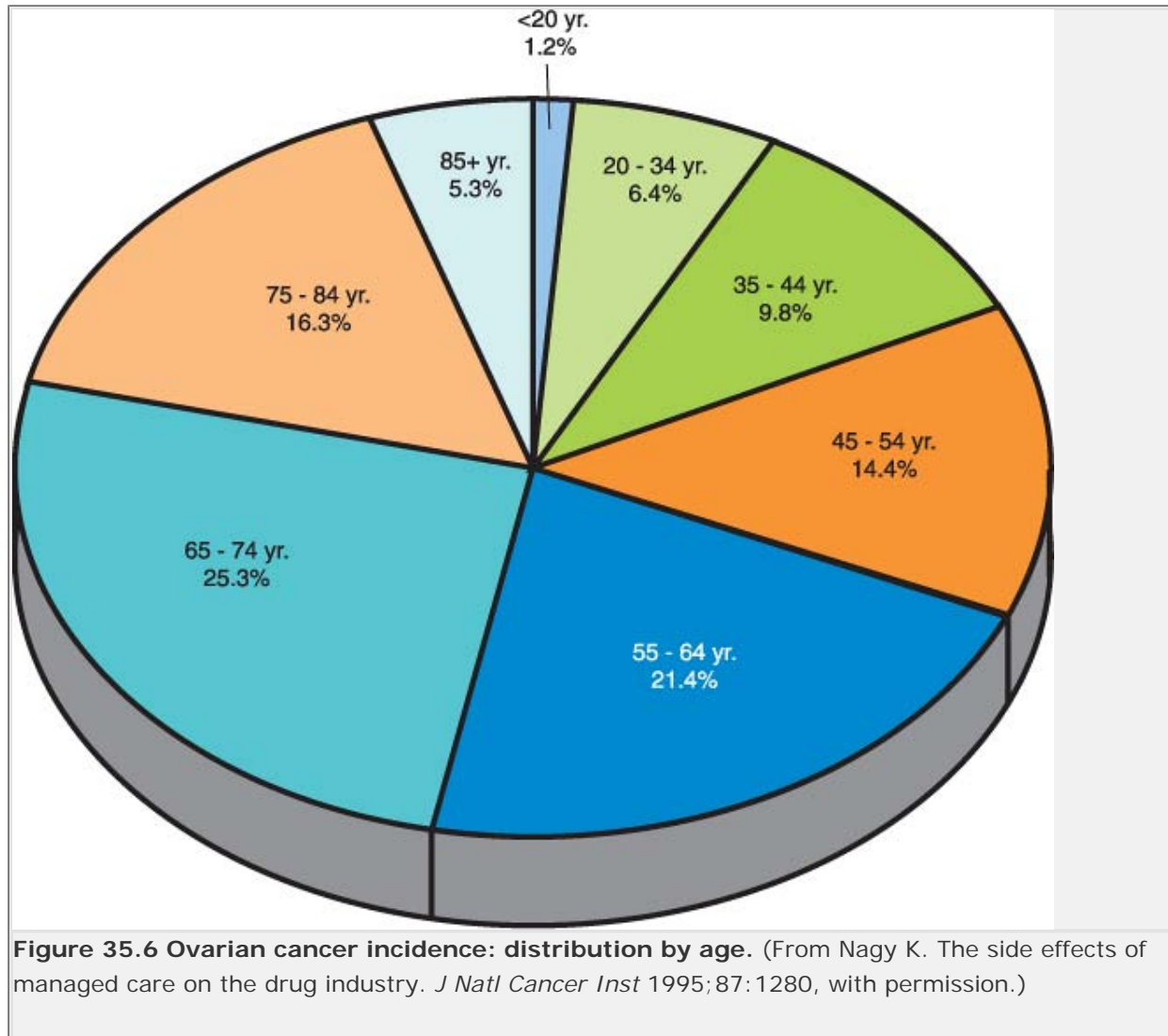
The peak incidence of invasive epithelial ovarian cancer is at 56 to 60 years of age (2,3,24). The age-specific incidence of ovarian epithelial cancer rises precipitously from 20 to 80 years of age and subsequently declines (24). These cancers are relatively uncommon in women younger than age 45. Fewer than 1% of epithelial ovarian cancers occur before the age of 21 years, two thirds of ovarian malignancies in such patients being germ cell tumors (2,24,25). **About 30% of ovarian neoplasms in postmenopausal women are malignant, whereas only about 7% of ovarian epithelial tumors in premenopausal patients are frankly malignant** (2,3).

The average age of patients with borderline tumors is approximately 46 years (2,3,5). Eighty to ninety percent of ovarian cancers, including borderline forms, occur after the age of 40 years, whereas 30% to 40% of malignancies occur after the age of 65 years. The chance that a primary epithelial tumor will be of borderline or invasive malignancy in a patient younger than 40 years is approximately 1 in 10, but after that age it rises to one in three (2,3). Fewer than 1% of epithelial ovarian cancers occur before the age of 20 years, with two thirds of ovarian malignancies in such patients being germ cell tumors.

Etiology

Ovarian cancer has been associated with low parity and infertility (26). Although there have been a variety of epidemiologic variables correlated with ovarian cancer, such as talc use, galactose consumption, and tubal ligation (see Chapter 4), none has been so strongly correlated as prior reproductive history and duration of the reproductive career (26,27). Early menarche and late menopause increase the risk of ovarian cancer (27). These factors and the relationship of parity and infertility to the risk of ovarian cancer have led to the hypothesis that suppression of ovulation may be an important factor. **Theoretically,**

this process might lead to a higher probability of spontaneous mutations that can unmask germline mutations or otherwise lead to the oncogenic phenotype (see Chapter 6).



Prevention

Because parity is inversely related to the risk of ovarian cancer, having at least one child is protective of the disease, with a risk reduction of 0.3 to 0.4. Oral contraceptive use reduces the risk of epithelial ovarian cancer (26). Women who use oral contraceptives for 5 or more years reduce their relative risk to 0.5 (i.e., there is a

50% reduction in the likelihood of development of ovarian cancer). Women who have had two children and have used oral contraceptives for 5 or more years have a relative risk of ovarian cancer as low as 0.3, or a 70% reduction (28). **Therefore, the oral contraceptive pill is the only documented method of chemoprevention for ovarian cancer, and it should be recommended to women for this purpose. When counseling patients regarding birth control options, this important benefit of oral contraceptive use should be emphasized. This is also important for women with a strong family history of ovarian cancer** (see discussion below).

Fenretinide (4-hydroxyretinoic acid), a vitamin A derivative, has been given to women with unilateral breast cancer in an effort to reduce the risk of contralateral breast cancer. In a prospective, randomized, placebo-controlled trial conducted in Italy (29), women with unilateral breast cancer were given for 6 months either *fenretinide* orally or a placebo. In the treatment group, no ovarian cancers developed, whereas there were six cases of ovarian cancer in the control group. A larger trial is ongoing in an attempt to verify these data.

The performance of a prophylactic salpingo-oophorectomy reduces, but does not eliminate, the risk of ovarian and fallopian tube cancers (19,22). Because the entire peritoneum is at risk, peritoneal carcinomas can occur even after prophylactic

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oophorectomy. **In premenopausal women at low risk for ovarian cancer, a thorough discussion of the risks and benefits of oophorectomy should be undertaken. The ovaries may provide protection from cardiovascular and orthopedic diseases, and long-term mortality may not be decreased by the performance of prophylactic oophorectomy** (30).

Screening

The value of tumor markers and ultrasonography to screen for epithelial ovarian cancer has not been clearly established by prospective studies. Screening results with transabdominal ultrasonography have been encouraging (31,32,33), but specificity has been limited. However, advances in transvaginal ultrasonography have been shown to have a very high (>95%) sensitivity for the detection of early-stage ovarian cancer, although this test alone might require as many as 10 to 15 laparotomy procedures be performed for each case of ovarian cancer detected (31,32). Routine annual pelvic examinations have had disappointing results in the early detection of ovarian cancer (34). Transvaginal color-flow Doppler to assess the vascularity of the ovarian vessels has been shown to be a useful adjunct to ultrasonography (35,36), but it has not been shown to be useful in screening.

CA125 has been shown to contribute to the early diagnosis of epithelial ovarian cancer (37,38,39,40,41,42,43). **Regarding the sensitivity of the test, CA125 can detect 50% of patients with stage I disease** (37,42). **Data suggest that the specificity of CA125 is improved when the test is combined with transvaginal ultrasonography** (44) or

when the CA125 levels are followed over time (43,44). These data have encouraged the development of prospective screening studies in Sweden and the United Kingdom (39,40). In these studies, patients with elevated CA125 levels (>30 U/mL) have undergone abdominal ultrasonography, and 14 ovarian cancers have been discovered among 27,000 women screened. About four laparotomies were performed for each case of cancer detected.

A randomized trial of nearly 22,000 women aged 45 years or older was performed in the United Kingdom (44). **The patients were assigned to either a control group of routine pelvic examination** (n = 10,977) **or to a screening group** (n = 10,958). The screening consisted of three annual screens that involved measurement of serum CA125 levels, pelvic ultrasonography if the CA125 was 30 U/mL or higher, and referral for gynecologic examination if the ovarian volume was 8.8 mL or greater on the ultrasonography. Of the 468 women in the screened group with an elevated CA125, 29 were referred for surgery, six cancers were discovered, and 23 had false-positive screening results, yielding a positive predictive value of 20.7%. During a 7-year follow-up period, cancer developed in 10 additional women in the screened group, as it did in 20 women in the control group. Although the median survival of women in whom cancer developed in the screened group was 72.9 months, compared with 41.8 months in the control group ($p = 0.0112$), the number of deaths did not differ significantly between the control and screened groups (18/10,977 versus 9/10,958; relative risk 2.0 [0.78 to 5.13]). Therefore, these data show that a multimodal approach to ovarian cancer screening is feasible, but a larger trial is necessary to determine whether this approach affects mortality. Such a three-arm randomized trial is ongoing in the United Kingdom, and the anticipated accrual is approximately 50,000 women per study arm and 100,000 women in the control arm. Based on the risk of ovarian cancer (ROC) algorithm, patients in the third group will be referred for transvaginal ultrasonography and/or surgery (45). Women will be screened for 3 years and studied for 7 years. **This trial may demonstrate more definitively the feasibility of screening for ovarian cancer as well as the impact of early detection on survival.**

A new approach is the use of proteomic patterns to identify ovarian cancer using surface-enhanced laser desorption ionization time-of-flight (SELDI-TOF) technology

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(46). In a study using this technology, the sensitivity for predicting ovarian cancer was 100% with a specificity of 95% and a positive predictive value of 94%. The assay correctly identified all 18 women with stage I tumors. This technology is in the early phases of development and validation, and its efficacy has yet to be demonstrated in large population-based studies.

Another new approach is the measurement of *plasma DNA levels* and *allelic imbalance* by a technique known as digital single nucleotide polymorphism (SNP) analysis. In a study by Chang et al. (47), this analysis had a 87% (13 of 15) positive correlation in stages I and II patients, and a 95% (37 of 39) correlation in patients with stages III and IV disease.

Given the false-positive results for both CA125 and transvaginal

ultrasonography, particularly in premenopausal women, these tests are not cost-effective and should not be used routinely to screen for ovarian cancer (48). In the future, new markers or technologies may improve the specificity of ovarian cancer screening, but proof of this will require a large, prospective study (41,42). Screening in women who have a familial risk may have a better yield, but additional study is necessary (48,49).

Genetic Risk for Epithelial Ovarian Cancer

The lifetime risk of ovarian carcinoma for women in the United States is about 1.4% (1,2,3). The risk of ovarian cancer is higher than that in the general population in women with certain family histories (50,51,52,53,54,55,56,57,58,59). **Most epithelial ovarian cancer is sporadic, with familial or hereditary patterns accounting for 5% to 10% of all malignancies** (51).

Hereditary Ovarian Cancer

BRCA1 and BRCA2

Most hereditary ovarian cancer is associated with mutations in them *BRCA1* gene, located on chromosome 17 (50). **A small proportion of inherited disease is associated with germline mutations in another gene, *BRCA2*, located on chromosome 13** (52). Discovered through linkage analyses, these two genes are associated with the genetic predisposition to both ovarian and breast cancer. There may be other yet undiscovered genes that predispose to ovarian and breast cancer (59).

In the past, it had been thought that there were two distinct syndromes associated with a genetic risk, *site-specific hereditary ovarian cancer* and *hereditary breast-ovarian cancer syndrome*. However, it is now believed that these groups essentially represent a continuum of mutations with different degrees of penetrance within a given family (54,59). In addition, there is a higher-than-expected risk of ovarian and endometrial cancer in the *Lynch II syndrome*, known also as the ***hereditary nonpolyposis colorectal cancer syndrome (HNPCC syndrome)*** (60).

The mutations are inherited in an autosomal dominant fashion, and therefore a full pedigree analysis (i.e., both maternal and paternal sides of the family) must be carefully evaluated (54). There are numerous distinct mutations that have been identified on each of these genes, and the mutations have different degrees of penetrance that may account for the preponderance of either breast cancer, ovarian cancer, or both, in any given family. **Based on analysis of women who have a mutation in the *BRCA1* gene and are from high-risk families, the lifetime risk of ovarian cancer may be as high as 28% to 44%, and the risk has been calculated to be as high as 27% for those women with a *BRCA2* mutation** (51,52,58). **The risk of breast cancer in women with a *BRCA1* or *BRCA2***

Hereditary ovarian cancers in general occur in women approximately 10 years younger than those with nonhereditary tumors (51). Because the median age of epithelial ovarian cancer is in the mid- to late 50s, a woman with a first- or second-degree relative who had premenopausal ovarian cancer may have a higher probability of carrying an affected gene.

Breast and ovarian cancer may exist in a family in which there is a combination of epithelial ovarian and breast cancers, affecting a mixture of first- and second-degree relatives. Women with this syndrome tend to have these tumors at a young age, and the breast cancers may be bilateral. If two first-degree relatives are affected, this pedigree is consistent with an autosomal dominant mode of inheritance (44,50).

Founder Effect

There is a higher carrier rate of *BRCA1* and *BRCA2* mutations in women of Ashkenazi Jewish descent and in Icelandic women (56,57,59). There have been three specific mutations carried by the Ashkenazi population, 185delAG and 5382insC on *BRCA1*, and 6174 delT on *BRCA2*. **The total carrier rate for a patient of Ashkenazi Jewish descent to have at least one of these three mutations is 1 in 40, or 2.5%**, and thus there is a substantial risk in this population. The increased risk is a result of the *founder effect*, in which a higher rate of mutations occurs in a defined geographic area.

Pedigree Analysis

The risk of carrying a germline mutation that predisposes to ovarian cancer depends on the number of first- and/or second-degree relatives (or both) with a history of epithelial ovarian carcinoma or breast cancer (or both), and on the number of malignancies that occur at an earlier age. The degree of risk is difficult to determine precisely unless a full pedigree analysis is performed.

- **In families with two first-degree relatives (i.e., mother, sister, or daughter) with documented premenopausal epithelial ovarian cancer, the risk that a female first-degree relative has an affected gene could be as high as 35% to 40%** (52).
- **In families with a single first-degree relative and a single second-degree relative (i.e., grandmother, aunt, first cousin, or granddaughter) with epithelial ovarian cancer, the risk that a woman has an affected gene also may be increased. The risk may be two- to 10-fold higher than in those without a familial history of the disease** (52).

- **In families with a single postmenopausal first-degree relative with epithelial ovarian carcinoma, a woman may not have an increased risk of having an affected gene because the case is most likely to be sporadic. However, if the ovarian cancer occurs in a premenopausal relative, this could be significant, and a full pedigree analysis should be undertaken.**
- **Women with a primary history of breast cancer have twice the expected incidence of subsequent ovarian cancer (51).**

Hereditary Nonpolyposis Colon Cancer, or Lynch II Syndrome

HNPCC syndrome, which includes multiple adenocarcinomas, involves a combination of familial colon cancer (known as the Lynch I syndrome); a high rate of ovarian, endometrial, and breast cancers; and other malignancies of the gastrointestinal and genitourinary systems (60). The mutations that have been associated with this syndrome

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are *MSH2*, *MLH1*, *PMS1*, and *PMS2*. The risk that a woman who is a member of one of these families will develop epithelial ovarian cancer depends on the frequency of this disease in first- and second-degree relatives, although these women appear to have at least 3 times the relative risk of the general population. A full pedigree analysis of such families should be performed by a geneticist to determine the risk more accurately.

Management of Women at High Risk for Ovarian Cancer

The management of a woman with a strong family history of epithelial ovarian cancer must be individualized and depends on her age, her reproductive plans, and the extent of risk. In all of these syndromes, women at risk benefit from a thorough pedigree analysis. A geneticist should evaluate the family pedigree for at least three generations. Decisions about management are best made after careful study and, whenever possible, verification of the histologic diagnosis of the family members' ovarian cancer.

The value of testing for *BRCA1* and *BRCA2* has been clearly established, and there are guidelines for testing (54,59,61). The importance of genetic counseling cannot be overemphasized because the decision is complex. The American Society of Clinical Oncology has offered guidelines that emphasize careful evaluation by geneticists, careful maintenance of medical records, and a clear understanding in a genetic screening clinic of how to counsel and manage these patients. Concerns remain over how the information should be used, the

impact on insurability, how the results will be interpreted, and how the information will be used within a specific family (e.g., to counsel children).

Although there are some conflicting data, the behavior of breast cancers arising in women with germline mutations in *BRCA1* or *BRCA2* is comparable to that of sporadic tumors (53). **Women with breast cancer who carry these mutations, however, are at a greatly increased risk of ovarian cancer as well as a second breast cancer: the lifetime risk of ovarian cancer is 54% for women who have a *BRCA1* mutation and 23% for those with a *BRCA2* mutation, and for the two groups together, there is an 82% lifetime risk of breast cancer** (62).

Although recommended by the National Institutes of Health Consensus Conference on Ovarian Cancer (63), **the value of screening with transvaginal ultrasonography, CA125 levels, or other procedures has not been clearly established in women at high risk.** Bourne and co-workers (49) have shown that, using this approach, tumors can be detected approximately 10 times more often than in the general population, and thus they recommend screening in high-risk women.

Data derived from a multicenter consortium of genetic screening centers indicate that the use of the oral contraceptive pill is associated with a lower risk for development of ovarian cancer in women who have a mutation in either *BRCA1* or *BRCA2* (64). The risk reduction is significant: in women who have taken oral contraceptives for 5 or more years, the relative risk of ovarian cancer is 0.4, or a 60% reduction in the incidence of the disease.

Prophylactic Oophorectomy in High-risk Women

The value of prophylactic salpingo-oophorectomy in these patients has been documented (65,66,67,68,69,70,71). Women at high risk for ovarian cancer who undergo prophylactic oophorectomy have a risk of harboring occult neoplasia: in one series of 98 such operations, 3 (3.1%) patients had a low-stage ovarian malignancy (67). **The protection against ovarian cancer is excellent: the performance of a prophylactic salpingo-oophorectomy reduced the risk of *BRCA*-related gynecologic cancer by 96%** (68). Although the risk of ovarian cancer is significantly diminished, there remains the small risk of peritoneal carcinoma, a tumor for which women who have mutations in *BRCA1* and *BRCA2* may have a higher predisposition. In these series, the subsequent development of peritoneal

carcinoma was 0.8% and 1 %, respectively (66,67). **In addition, the risk of developing subsequent breast cancer was reduced by 50% to 80%.** Women at high risk for ovarian cancer who undergo prophylactic oophorectomy have a risk of harboring occult neoplasia. In one series of 42 such operations, four patients (9.5%) had a malignancy, one of which was noted at surgery and three that were microscopic; all were smaller than 5 mm (66).

The role of hysterectomy is more controversial. Although most studies show no increase in

the rate of uterine and cervical tumors, there are some reports of an increase of papillary serous tumors of the endometrium (71). Women on *tamoxifen* are at higher risk for benign endometrial lesions (e.g., polyps) and endometrial cancer. Therefore, **it is reasonable to consider the performance of a prophylactic hysterectomy in conjunction with salpingo-oophorectomy**, and this decision should be individualized.

The survival of women who have a *BRCA1* or *BRCA2* mutation and develop ovarian cancer is longer than that for those who do not have a mutation. In one study, the median survival for mutation carriers was 53.4 months compared with 37.8 months for those with sporadic ovarian cancer from the same institution (72).

Recommendations

Current recommendations for management of women at high risk for ovarian cancer are summarized as follows (61,63,70):

- **Women who appear to be at high risk for ovarian or breast cancer should undergo genetic counseling and, if the risk appears to be substantial, may be offered genetic testing for *BRCA1* and *BRCA2*.**
- **Women who wish to preserve their reproductive capacity can undergo screening by transvaginal ultrasonography every 6 months**, although the efficacy of this approach is not clearly established.
- **Oral contraceptives should be recommended** to young women before they embark on an attempt to have a family.
- **Women who do not wish to maintain their fertility or who have completed their families should be recommended to undergo prophylactic bilateral salpingo-oophorectomy.** The risk should be clearly documented, preferably established by *BRCA1* and *BRCA2* testing, before oophorectomy is performed. These women should be counseled that this operation does not offer absolute protection, because peritoneal carcinomas occasionally can occur after bilateral oophorectomy (19,22,71).
- **In women who also have a strong family history of breast or ovarian cancer, annual mammographic screening should be performed beginning at age 30 years.**
- **Women with a documented HNPCC syndrome should be treated as above, but in**

and endometrial biopsy (60,68).

Symptoms

The majority of women with epithelial ovarian cancer have vague and nonspecific symptoms. (3,73,74,75). In early-stage disease, the patient may experience irregular menses if she is premenopausal. If a pelvic mass is compressing the bladder or rectum, she may report urinary frequency or constipation (73,74,75). Occasionally, she may perceive lower

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abdominal distention, pressure, or pain, such as dyspareunia. Acute symptoms, such as pain secondary to rupture or torsion, are unusual.

In advanced-stage disease, patients most often have symptoms related to the presence of ascites, omental metastases, or bowel metastases. The symptoms include abdominal distention, bloating, constipation, nausea, anorexia, or early satiety. Premenopausal women may report irregular or heavy menses, whereas vaginal bleeding may occur in postmenopausal women (72). In one survey of 1,725 with ovarian cancer, 95% recalled symptoms before diagnosis, including 89% with stage I and II disease and 97% with stages III and IV disease (74). Some 70% had abdominal or gastrointestinal symptoms, 58% pain, 34% urinary symptoms, and 26% pelvic discomfort.

Signs

The most important sign of epithelial ovarian cancer is the presence of a pelvic mass on physical examination. A solid, irregular, fixed pelvic mass is highly suggestive of an ovarian malignancy. If, in addition, an upper abdominal mass or ascites is present, the diagnosis of ovarian cancer is almost certain. Because the patient usually reports abdominal symptoms, she may not have a pelvic examination, and a tumor may be missed.

In patients who are at least 1 year past menopause, the ovaries should have become atrophic and not palpable. It has been proposed that any palpable pelvic mass in these patients should be considered potentially malignant, a situation that has been referred to as the postmenopausal palpable ovary syndrome (76). This concept has been challenged, because subsequent authors have reported that only about 3% of palpable masses measuring <5 cm in postmenopausal women are malignant (49).

Diagnosis

Ovarian epithelial cancers must be differentiated from benign neoplasms and functional cysts of the ovaries. A variety of benign conditions of the reproductive tract, such as pelvic inflammatory disease, endometriosis, and pedunculated uterine leiomyomas, can simulate

ovarian cancer. Nongynecologic causes of a pelvic tumor, such as an inflammatory (e. g., diverticular) disease or neoplastic colonic mass, must be excluded (3). A pelvic kidney can simulate ovarian cancer.

Serum CA125 levels have been shown to be useful in distinguishing malignant from benign pelvic masses (77). For a postmenopausal patient with an adnexal mass and a very high serum CA125 level (>200 U/mL), there is a 96% positive predictive value for malignancy. For premenopausal patients, however, the specificity of the test is low because the CA125 level tends to be elevated in common benign conditions.

For the premenopausal patient, a period of observation is reasonable provided the adnexal mass does not have characteristics that suggest malignancy (i.e., it is mobile, mostly cystic, unilateral, and of regular contour). Generally, an interval of no more than 2 months is allowed, during which hormonal suppression with the oral contraceptive may be used. If the lesion is not neoplastic it should regress, as measured by pelvic examination and pelvic ultrasonography. If the mass does not regress or if it increases in size, it must be presumed to be neoplastic and must be removed surgically.

The size of the lesion is important. If a cystic mass is >8 cm in diameter, the probability is high that the lesion is neoplastic, unless the patient has been taking clomiphene citrate or other agents to induce ovulation (31,32,33,34). Patients whose lesions are suggestive of malignancy (i.e., predominantly solid, relatively fixed, or irregularly shaped) should undergo laparotomy, as should postmenopausal patients with adnexal masses.

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Ultrasonographic signs of malignancy include an adnexal pelvic mass with areas of complexity, such as irregular borders, multiple echogenic patterns within the mass, and dense multiple irregular septae. Bilateral tumors are more likely to be malignant, although the individual characteristics of the lesions are of greater significance.

Transvaginal ultrasonography may have a somewhat better resolution than transabdominal ultrasonography for adnexal neoplasms (78,79,80,81). Doppler color flow imaging may enhance the specificity of ultrasonography for demonstrating findings consistent with malignancy (82,83,84).

In the premenopausal patient, a period of observation is reasonable, provided the adnexal mass is not clinically suspicious (i.e., it is mobile, mostly cystic, unilateral, and of regular contour). Generally, an interval of 2 months is allowed for observation. The size of the lesion is of importance. If a complex cystic mass is more than 8 to 10 cm in diameter, the probability is high that the lesion is neoplastic, unless the patient has been taking *clomiphene citrate* or other agents to induce ovulation (85,86,87). If the lesion is not neoplastic, it should remain stable or regress, as measured by pelvic examination and pelvic ultrasonography. If a mass does not regress, or if it increases in size or complexity, it must be presumed to be neoplastic and removed surgically.

In postmenopausal women with unilocular cysts measuring 8 to 10 cm or less and normal serial CA125 levels, expectant management is acceptable, and this approach may decrease the number of surgical interventions (85,86,87).

Premenopausal patients whose lesions are clinically suspicious (i.e., large, predominantly solid, relatively fixed, or irregularly shaped) should undergo laparotomy, as should postmenopausal patients with complex adnexal masses of any size.

The diagnosis of an ovarian cancer requires an exploratory laparotomy. The preoperative evaluation of the patient with an adnexal mass is outlined in Figure 14.20 (see Chapter 14).

Before the planned exploration, the patient should undergo routine hematologic and biochemical assessments. A preoperative evaluation in a patient undergoing laparotomy should include a radiograph of the chest. Abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) are of limited value for a patient with a definite pelvic mass (88,89,90). A CT or MRI should be performed for patients with ascites and no pelvic mass to look for liver or pancreatic tumors. The findings only rarely preclude laparotomy (88). The value of PET scanning is still being evaluated (91,92). If the hepatic enzyme values are normal, the likelihood of liver disease is low. Liver-spleen scans, bone scans, and brain scans are unnecessary unless symptoms or signs suggest metastases to these sites.

The preoperative evaluation should exclude other primary cancers metastatic to the ovary. A barium enema or colonoscopy is indicated in selected patients with symptoms and signs suspicious for colon cancer. This study should be performed for any patient who has evidence of occult blood in the stool or of intestinal obstruction. An upper gastrointestinal radiographic series or gastroscopy is indicated if there are upper gastrointestinal symptoms such as nausea, vomiting, or hematemesis (3,93). Bilateral mammography is indicated if there is any breast mass, because occasionally breast cancer metastatic to the ovaries can simulate primary ovarian cancer.

A Pap test should be performed, although its value for the detection of ovarian cancer is very limited. Patients who have irregular menses or postmenopausal vaginal bleeding should have endometrial biopsy and endocervical curettage to exclude the presence of uterine or endocervical cancer metastatic to the ovary.

Differential Diagnosis

Ovarian epithelial cancers must be differentiated from benign neoplasms and functional cysts of the ovaries (85,86,87). **A variety of benign conditions of the reproductive tract, such as pelvic inflammatory disease, endometriosis, and pedunculated uterine leiomyomata, can simulate ovarian cancer.** Nongynecologic causes of a pelvic tumor, such as an inflammatory or neoplastic colonic mass, must be excluded (94). A pelvic kidney can

simulate ovarian cancer.

Patterns of Spread

Ovarian epithelial cancers spread primarily by exfoliation of cells into the peritoneal cavity, by lymphatic dissemination, and by hematogenous spread.

Transcoelomic

The most common and earliest mode of dissemination of ovarian epithelial cancer is by exfoliation of cells that implant along the surfaces of the peritoneal cavity. The cells tend to follow the circulatory path of the peritoneal fluid. The fluid tends to move with the forces of respiration from the pelvis, up the paracolic gutters, especially on the right, along the intestinal mesenteries, to the right hemidiaphragm. Therefore, metastases are typically seen on the posterior cul-de-sac, paracolic gutters, right hemidiaphragm, liver capsule, the peritoneal surfaces of the intestines and their mesenteries, and the omentum. The disease seldom invades the intestinal lumen but progressively agglutinates loops of bowel, leading to a functional intestinal obstruction. This condition is known as carcinomatous ileus (3).

Lymphatic

Lymphatic dissemination to the pelvic and para-aortic lymph nodes is common, particularly in advanced-stage disease (95,96,97). Spread through the lymphatic channels of the diaphragm and through the retroperitoneal lymph nodes can lead to dissemination above the diaphragm, especially to the supraclavicular lymph nodes (95). Burghardt et al. (97) reported that 78% of patients with stage III disease have metastases to the pelvic lymph nodes. In another series (95), the rate of para-aortic lymph nodes positive for metastasis was 18% in stage I, 20% in stage II, 42% in stage III, and 67% in stage IV.

Hematogenous

Hematogenous dissemination at the time of diagnosis is uncommon. Spread to vital organ parenchyma, such as the lungs and liver, occurs in only about 2% to 3% of patients. Most patients with disease above the diaphragm when diagnosed have a right pleural effusion (3). Systemic metastases are seen more frequently in patients who have survived for some years. Dauplat et al. (98) reported that distant metastasis consistent with stage IV disease ultimately occurred in 38% of the patients whose disease was originally intraperitoneal.

Prognostic Factors

The outcome of treatment can be evaluated in the context of prognostic factors, which can be grouped into pathologic, biologic, and clinical factors (99).

Pathologic Factors

The morphology and histologic pattern, including the architecture and grade of the lesion, are important prognostic variables (3). Histologic type has not generally been believed to be of prognostic significance, but several papers recently have contained suggestions that clear cell carcinomas are associated with a prognosis worse than that of other histologic types (99,100).

Histologic grade, as determined either by the pattern of differentiation or by the extent of cellular anaplasia and the proportion of undifferentiated cells, seems to be of prognostic significance (101,102,103,104). However, studies of the reproducibility of grading ovarian cancers

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have shown a high degree of intraobserver and interobserver variation (105,106). **Because there is significant heterogeneity of tumors and observational bias, the value of histologic grade as an independent prognostic factor has not been clearly established.** Baak et al. (107) have presented a standard grading system based on morphometric analysis, and the system seems to correlate with prognosis, especially in its ability to distinguish low-grade or borderline patterns from other tumors.

Biologic Factors

Several biologic factors have been correlated with prognosis in epithelial ovarian cancer. Using flow cytometry, Friedlander et al. (108) showed that ovarian cancers were commonly aneuploid. Furthermore, they and others showed that there was a high correlation between FIGO stage and ploidy; low-stage cancers tend to be diploid and high-stage tumors tend to be aneuploid (108,109,110,111,112). **Patients with diploid tumors have a significantly longer median survival than those with aneuploid tumors:** 5 years versus 1 year, respectively (108). Multivariate analyses have demonstrated that **ploidy is an independent prognostic variable** and one of the most significant predictors of survival (108). Flow cytometric analysis also provides data on the cell cycle, and the proliferation fraction (S phase) determined by this technique has correlated with prognosis in some studies (108,109,110,111,112).

More than 100 proto-oncogenes have been identified, and studies have focused on the amplification or expression of these genetic loci and their relationship to the development and progression of ovarian cancer (113,114). For example, Slamon et al. (115) reported that 30% of epithelial ovarian tumors expressed HER-2/*neu* oncogene and that this group had a poorer prognosis, especially patients with more than five copies of the gene. Berchuck et al. (116) reported a similar incidence (32%) of HER-2/*neu* expression. In their series, patients whose tumors expressed the gene had a poorer median survival (15.7 months versus 32.8 months). Others have not substantiated this

finding (117,118,119,120,121,122), and a review of the literature by Leary et al. (118) revealed an overall incidence of HER-2/*neu* expression of only 11%. Thus, **the prognostic value of HER-2/*neu* expression in ovarian cancer is unclear, and further study is required.**

The most commonly expressed tumor suppressor gene in ovarian cancer is *p53* (123,124,125). Indeed, as many as one half of all epithelial ovarian cancers have evidence of mutated *p53* in the tumor. Other tumor suppressor genes that are being evaluated are *ras* and *PTEN* (126,127,128).

The *in vitro* clonogenic assay has been studied in relation to ovarian cancer. A significant inverse correlation has been reported between clonogenic growth *in vitro* and survival (129,130,131). Multivariate analysis has found that clonogenic growth in a semisolid culture medium is a significant independent prognostic variable (131). The use of an **"extreme drug resistance assay"** has been suggested as a possible means of directing therapy by defining platinum-sensitive and resistant tumors *in vitro* (132). **Further study will be needed to evaluate the clinical usefulness of these assays.**

Clinical Factors

In addition to stage, the extent of residual disease after primary surgery, the volume of ascites, patient age, and performance status are all independent prognostic variables (133,141). Among patients with stage I disease, Dembo et al. (138) showed, in a multivariate analysis, that tumor grade and dense adherence to the pelvic peritoneum had a significant adverse impact on prognosis, whereas intraoperative tumor spillage or rupture did not. Sjövall et al. (139) confirmed that **ovarian cancers that undergo intraoperative rupture or spillage do not worsen prognosis, whereas tumors found to have already ruptured preoperatively do have a poorer prognosis.** A multivariate analysis of these and several other studies was performed by Vergote et al. (141), who found that **for early-stage disease, poor prognostic variables were tumor grade, capsular penetration, surface excrescences, and malignant ascites, but not iatrogenic rupture.**

Initial Surgery for Ovarian Cancer

Staging

Ovarian epithelial malignancies are staged according to the FIGO system listed in Table 35.2 (24). The FIGO staging is based on findings at surgical exploration. A preoperative evaluation should exclude the presence of extraperitoneal metastases.

The importance of thorough surgical staging cannot be overemphasized, because subsequent treatment will be determined by the stage of disease. For patients

in whom exploratory laparotomy does not reveal any macroscopic evidence of disease on inspection and palpation of the entire intra-abdominal space, a careful search for microscopic spread must be undertaken. In earlier series in which patients did not undergo careful surgical staging, the overall 5-year survival for patients with apparent stage I epithelial ovarian cancer was only about 60% (142). Since then, survival rates of 90% to 100% have been reported for patients who were properly staged and were found to have stage Ia or Ib disease (143,144).

Table 35.2 FIGO Staging for Primary Carcinoma of the Ovary

Stage I	Growth limited to the ovaries.
Ia	Growth limited to one ovary; no ascites containing malignant cells. No tumor on the external surface; capsule intact.
Ib	Growth limited to both ovaries; no ascites containing malignant cells. No tumor on the external surfaces; capsules intact.
Ic^a	Tumor either stage Ia or Ib but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both ovaries with pelvic extension.
IIa	Extension and/or metastases to the uterus and/or fallopian tubes.
IIb	Extension to other pelvic tissues.
IIc^a	Tumor either stage IIa or IIb but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.
IIIa	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
IIIb	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.
IIIc	Abdominal implants >2 cm in diameter or positive retroperitoneal or inguinal nodes or both.
Stage IV	Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

These categories are based on findings at clinical examination or surgical exploration or both. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

FIGO, International Federation of Obstetrics and Gynecology.

^a To evaluate the impact on prognosis of the different criteria for allotting cases to stage Ic or IIc, it would be of value to know if rupture of the capsule was (i) spontaneous or (ii) caused by the surgeon and if the source of malignant cells detected was (i) peritoneal washings or (ii) ascites.

Technique for Surgical Staging

In patients whose preoperative evaluation suggests a probable malignancy, a midline or paramedian abdominal incision is recommended to allow adequate access to the upper abdomen (3,142). When a malignancy is unexpectedly discovered in a patient who has a lower transverse incision, the rectus muscles can be either divided or detached from the symphysis pubis to allow better access to the upper abdomen. If this is not sufficient, the incision can be extended on one side to create a "J" incision (3).

The ovarian tumor should be removed intact, if possible, and a frozen histologic section should be obtained. If ovarian malignancy is present and the tumor is apparently confined to the ovaries or the pelvis, thorough surgical staging should be performed.

Staging involves the following steps (3,142):

- **Any free fluid, especially in the pelvic cul-de-sac, should be submitted for cytologic evaluation.**
- **If no free fluid is present, peritoneal washings should be performed by instilling and recovering 50 to 100 mL of saline from the pelvic cul-de-sac, each paracolic gutter, and beneath each hemidiaphragm.** Obtaining the specimens from under the diaphragms can be facilitated with the use of a rubber catheter attached to the end of a bulb syringe.
- **A systematic exploration of all the intra-abdominal surfaces and viscera is performed,** proceeding in a clockwise fashion from the cecum cephalad along the paracolic gutter and the ascending colon to the right kidney, the liver and gallbladder, the right hemidiaphragm, the entrance to the lesser sac at the para-aortic area, across the transverse colon to the left hemidiaphragm, down the left gutter and the descending colon to

the rectosigmoid colon. The small intestine and its mesentery from the Treitz ligament to the cecum should be inspected.

- **Any suspicious areas or adhesions on the peritoneal surfaces should be biopsied.** If there is no evidence of disease, multiple intraperitoneal biopsies should be performed. Tissue from the peritoneum of the pelvic cul-de-sac, both paracolic gutters, the peritoneum over the bladder, and the intestinal mesenteries should be taken for biopsy.
- **The diaphragm should be sampled either by biopsy or by scraping with a tongue depressor and obtaining a sample for cytologic assessment.** Biopsies of any irregularities on the surface of the diaphragm can be facilitated by use of the laparoscope and the associated biopsy instrument.
- **The omentum should be resected from the transverse colon, a procedure called an *infracolic omentectomy*.** The procedure is initiated on the underside of the greater omentum, where the peritoneum is incised just a few millimeters away from the transverse colon. The branches of the gastroepiploic vessels are clamped, ligated, and divided, along with all the small branching vessels that feed the infracolic omentum. If the gastrocolic ligament is palpably normal, it does not need to be resected.
- **The retroperitoneal spaces should be explored to evaluate the pelvic and para-aortic lymph nodes.** The retroperitoneal dissection is performed by incision of the peritoneum over the psoas muscles. This may be performed on the ipsilateral side only for unilateral tumors. Any enlarged lymph nodes should be resected and submitted for frozen section. If no metastases are present, a formal pelvic lymphadenectomy should be performed. The para-aortic area should be explored.

Results

Metastases in apparent stage I and II epithelial ovarian cancer occur in as many as 3 in 10 patients whose tumors appear to be confined to the pelvis but who have occult metastatic disease in the upper abdomen or the retroperitoneal lymph nodes (96,143,144,145,146,147,148,149,150,151,152). In a review of the literature (142), occult metastases were found in biopsies of the diaphragm in 7.3% of such patients, biopsies of the omentum in 8.6%, the pelvic lymph nodes in 5.9%, the aortic lymph nodes in 18.1%, and in 26.4% of peritoneal washings.

The importance of careful initial surgical staging is emphasized by the findings of a

cooperative national study (143) in which 100 patients with apparent stage I and II disease who were referred for subsequent therapy underwent additional surgical staging. In this series, 28% of the patients initially believed to have stage I disease were "upstaged" and 43% of those believed to have stage II disease had more advanced lesions. **A total of 31% of the patients were upstaged as a result of additional surgery, and 77% were reclassified as having stage III disease. Histologic grade was a significant predictor of occult metastasis.** Sixteen percent of the patients with grade 1 lesions were upstaged, compared with 34% with grade 2 disease and 46% with grade 3 disease.

Borderline Tumors

The principal treatment of borderline (low malignant potential) ovarian tumors is surgical resection of the primary tumor. There is no evidence that either subsequent chemotherapy or radiation therapy improves survival. **After a frozen section has determined that the histology is borderline, premenopausal patients who desire preservation of ovarian function may undergo a conservative operation, a unilateral oophorectomy (3,153,154).** In a study of patients who underwent unilateral ovarian cystectomy only for apparent stage I borderline serous tumors, Lim-Tan et al. (154) found that this conservative operation was also safe; only 8% of the patients had recurrences 2 to 18 years later, all with curable disease confined to the ovaries. Recurrence was associated with positive margins of the removed ovarian cyst (154). Thus, hormonal function and fertility can be maintained (3,153,154). For patients in whom an oophorectomy or cystectomy has been performed and a borderline tumor is later documented in the permanent pathology, no additional immediate surgery is necessary.

Stage I

After a comprehensive staging laparotomy, only a minority of women will have local disease (FIGO stage I). There are over 20,000 women diagnosed yearly with epithelial ovarian cancer in the United States, and nearly 4,000 of these have disease confined to the ovaries (1,155). The prognosis for these patients depends on the clinical-pathologic features, as outlined below. Because of this emphasis on the importance of surgical staging, the rate of lymph node sampling has increased in the United States, with a study showing that for women with stage I and II disease, the percentage having lymph nodes sampled increased from 38% to 59% from 1991 to 1996 (156).

The primary surgical treatment for stage I epithelial ovarian cancer is surgical, and patients should undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy, and surgical staging (142,143). In certain circumstances, a unilateral salpingo-oophorectomy may be performed. Based on the findings at surgery and the pathologic evaluation, patients with stage I ovarian cancer can be grouped into low-risk and high-risk categories (Table 35.3).

Stage I Low-risk

Fertility Preservation in Early-stage Ovarian Cancer

For patients who have undergone a thorough staging laparotomy and for whom there is no evidence of spread

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beyond the ovary, abdominal hysterectomy and bilateral salpingo-oophorectomy are appropriate therapy. The uterus and the contralateral ovary can be preserved in women with stage Ia, grade 1 to 2 disease who desire to preserve fertility.

The conditions of the women should be monitored carefully with routine periodic pelvic examinations and determinations of serum CA125 levels. Generally, the other ovary and the uterus are removed at the completion of childbearing.

Table 35.3 Prognostic Variables in Early-stage Epithelial Ovarian Cancer

<i>Low Risk</i>	<i>High Risk</i>
Low grade	High grade
Non—clear cell histologic type	Clear cell histologic type
Intact capsule	Tumor growth through capsule
No surface excrescences	Surface excrescences
No ascites	Ascites
Negative peritoneal cytologic findings	Malignant cells in fluid
Unruptured or intraoperative rupture	Preoperative rupture
No dense adherence	Dense adherence
Diploid tumor	Aneuploid tumor

From **Berek JS, Hacker NF**, eds. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005, with permission.

Guthrie et al. (152) studied the outcome of 656 patients with early-stage epithelial ovarian cancer. No untreated patients who had stage Ia, grade 1 cancer died of their disease; thus, adjuvant radiation and chemotherapy are unnecessary. Furthermore, the Gynecologic Oncology Group (GOG) carried out a prospective, randomized trial of observation versus *melphalan* for patients with stage Ia and Ib, grade 1–2 disease (100). Five-year survival for each group was 94% and 96%, respectively, confirming that no further treatment is needed for such patients.

Stage I High-risk

For patients whose disease is more poorly differentiated or in whom there are malignant cells either in ascitic fluid or in peritoneal washings, complete surgical

staging must be performed (3). The surgery should include the performance of a hysterectomy and bilateral salpingo-oophorectomy in addition to the staging laparotomy. Additional therapy is indicated, and although the optimal therapy for these patients is not known, most patients are treated with chemotherapy, as outlined below.

Advanced-Stage Ovarian Cancer

The surgical management of all patients with advanced-stage disease is approached in a similar manner, with modifications made for the overall status and general health of the patient, as well as the extent of residual disease present at the time treatment is initiated. A treatment scheme is outlined in Figure 35.7. Most patients subsequently receive combination chemotherapy for an empiric number of cycles.

Cytoreductive Surgery for Advanced-stage Disease

If the patient is medically stable, she should undergo cytoreductive surgery to remove as much of the tumor and its metastases as possible

(157,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184)

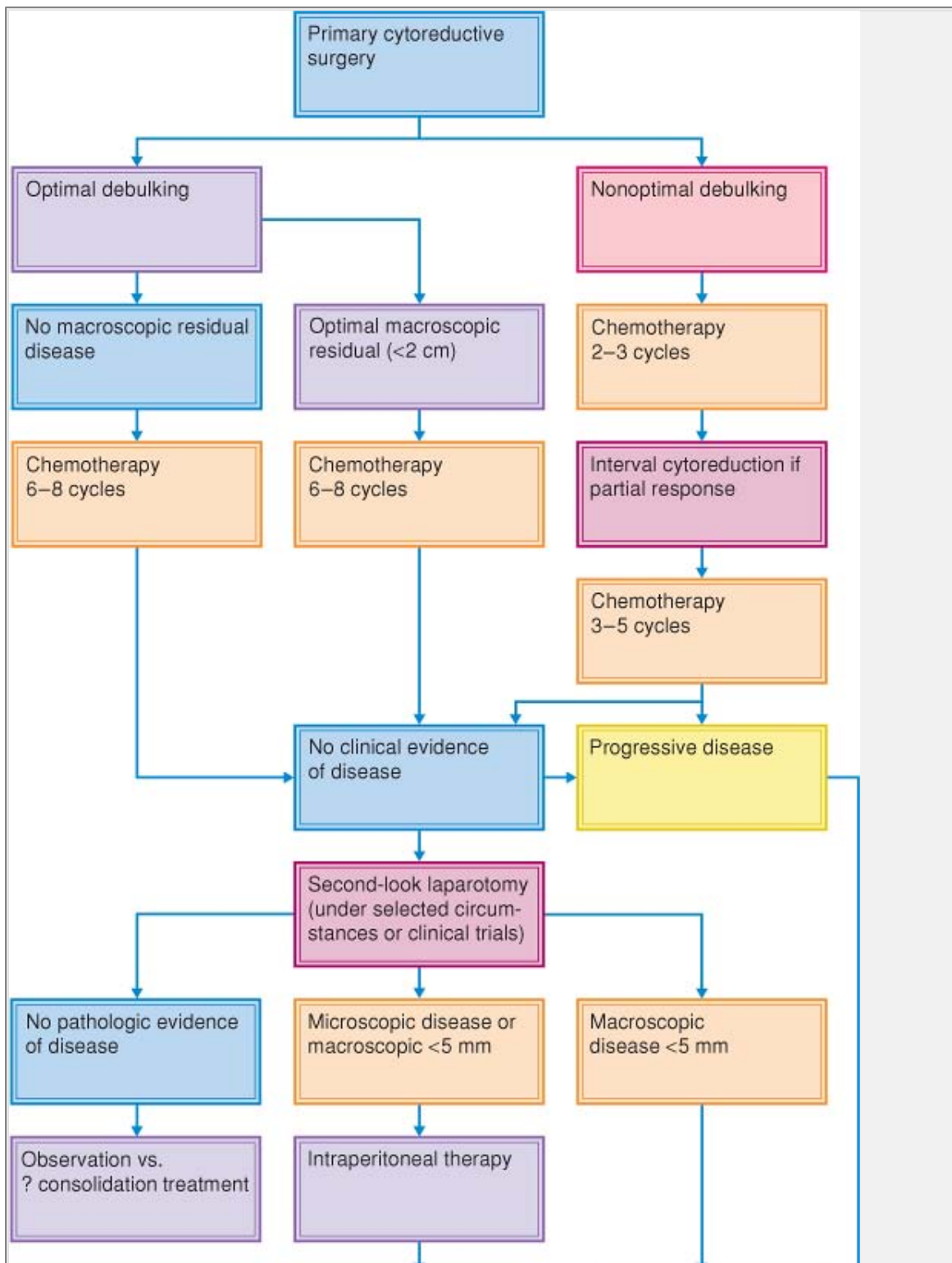
(see Fig 35.7). **The operation to remove the primary tumor as well as the associated metastatic disease is**

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referred to as "*debulking*" or cytoreductive surgery. The operation typically includes the performance of a total abdominal hysterectomy and bilateral salpingo-oophorectomy, along with a complete omentectomy and resection of any metastatic lesions from the peritoneal surfaces or from the intestines. The pelvic tumor often directly involves the rectosigmoid colon, the terminal ileum, and the cecum (Fig. 35.8). In a minority of

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patients, most or all of the disease is confined to the pelvic viscera and the omentum, so that removal of these organs will result in extirpation of all gross tumor, a situation that is associated with a reasonable chance of prolonged progression-free survival.



Clinical follow-up
? future surgical
evaluation

Experimental protocols
or palliative care

Figure 35.7 Treatment scheme for patients with advanced-stage ovarian cancer.

*Under selected circumstances or clinical trials. (From **Berek JS, Hacker NF.** *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005: 460, with permission.)

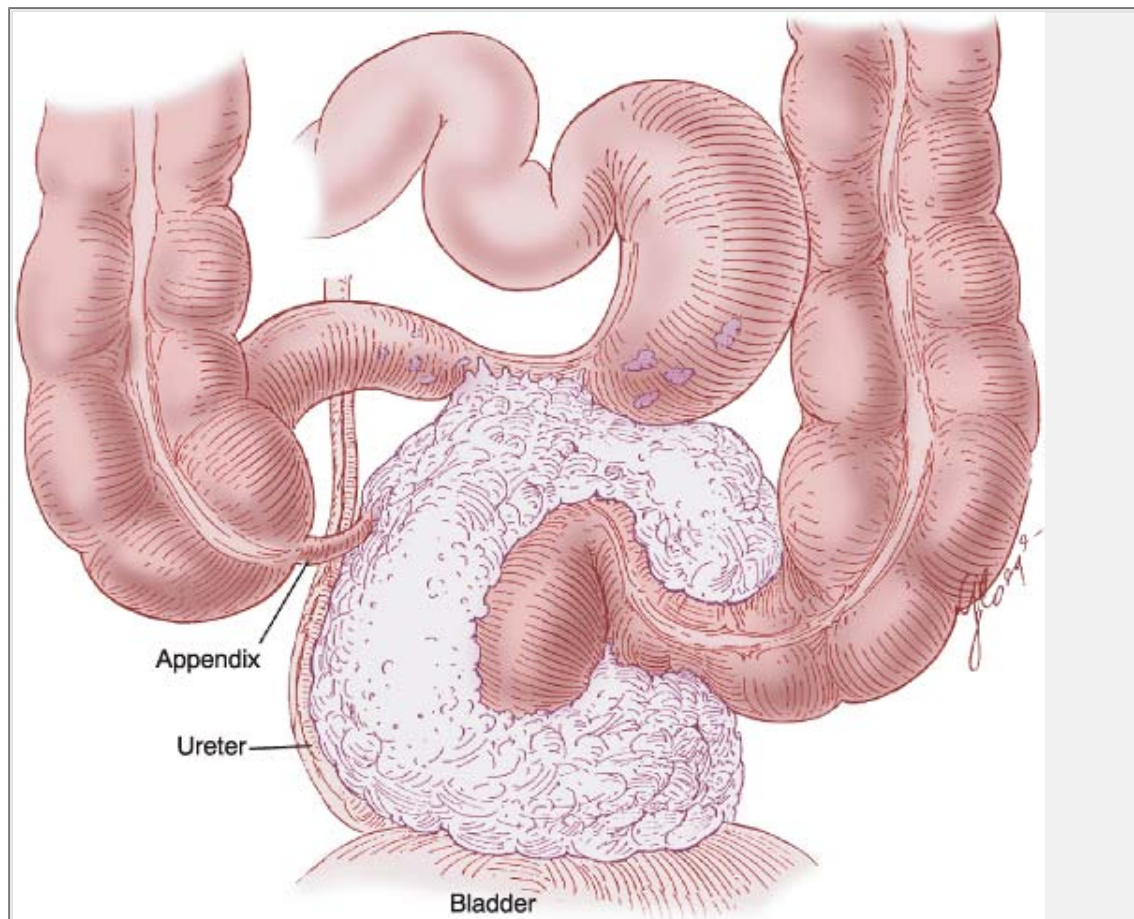


Figure 35.8 Extensive ovarian carcinoma involving the bladder, rectosigmoid, and ileocecal area. (From **Heintz APM, Berek JS.** *Cytoreductive surgery for ovarian carcinoma*. In: **Piver MS**, ed. *Ovarian malignancies*. Edinburgh, UK: Churchill Livingstone, 1987: 134, with permission.)

The removal of bulky tumor masses may reduce the volume of ascites present.

Often, ascites will completely disappear after removal of the primary tumor and a large omental "cake." Also, removal of the omental cake often alleviates the nausea and early satiety that many patients experience. Removal of intestinal metastases may restore adequate intestinal function and lead to an improvement in the overall nutritional status of the patient, thereby facilitating the patient's ability to tolerate subsequent chemotherapy.

A large, bulky tumor may contain areas that are poorly vascularized, and such areas will be exposed to suboptimal concentrations of chemotherapeutic agents. Similarly, these areas are poorly oxygenated, so that radiation therapy, which requires adequate oxygenation to achieve maximal cell kill, will be less effective. Thus, surgical removal of these bulky tumors may eliminate areas that are most likely to be relatively resistant to treatment.

In addition, larger tumor masses tend to be composed of a higher proportion of cells that are either nondividing or in the "resting" phase (i.e., G_0 cells, which are essentially resistant to the therapy). A low growth fraction is characteristic of bulky tumor masses, and cytoreductive surgery can result in smaller residual masses with a relatively higher growth fraction.

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Goals of Cytoreductive Surgery

The principal goal of cytoreductive surgery is removal of all of the primary cancer and, if possible, all metastatic disease. If resection of all metastases is not feasible, the goal is to reduce the tumor burden by resection of all individual tumors to an optimal status. Griffiths (157) initially proposed that all metastatic nodules should be reduced to <1.5 cm in maximal diameter and showed that survival was significantly longer in patients for whom this was achieved.

Subsequently, Hacker and Berek (158,159,160) showed that patients whose largest residual lesions were <5 mm had a superior survival rate, which was substantiated by Van Lindert et al. (161). The median survival of patients in this category was 40 months, compared with 18 months for patients whose lesions were <1.5 cm and 6 months for patients with nodules >1.5 cm. **Patients whose disease has been completely resected to no macroscopic (microscopic only) residual disease have the best overall survival** (162) (Fig. 35.9). **Approximately 60% of patients in this category will be free of disease at 5 years.**

The resectability of the metastatic tumor is usually determined by the location of the disease. Optimal cytoreduction is difficult to achieve in the presence of extensive disease on the diaphragm, in the parenchyma of the liver, along the base of the small-bowel mesentery, in the lesser omentum, or in the porta hepatis.

The ability of cytoreductive surgery to influence survival is limited by the extent of metastases before cytoreduction, presumably because of the presence of phenotypically resistant clones of cells in large metastatic masses. A patient

shorter survival than those with smaller areas of disease (160,162). Extensive carcinomatosis, the presence of ascites, and poor tumor grade, even with lesions that measure <5 mm, may also shorten the survival (163,164,165,166).

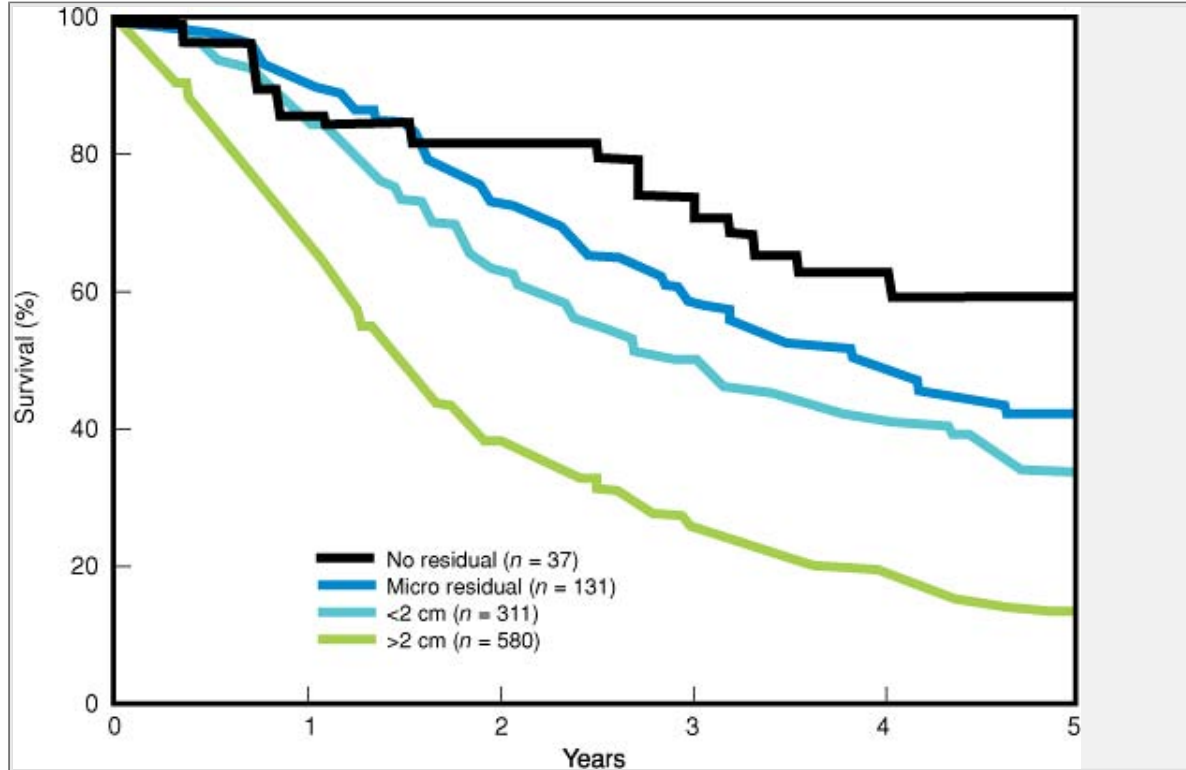


Figure 35.9 Survival of patients with stage IIIc epithelial ovarian cancer based on the maximal size of residual tumor after exploratory laparotomy and tumor resection.

(From Pecorelli S, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. Annual Report of the Results of Treatment of Gynaecological Cancer. *J Epidemiol Biostat* 1998; 3: 75–102, with permission.)

Exploration

The supine position on the operating table may be sufficient for surgical exploration of most patients. However, for those with extensive pelvic disease for whom a low resection of the colon may be necessary, the low lithotomy position should be used. Debulking operations should be performed through a vertical incision to gain adequate access to the upper abdomen as well as to the pelvis.

After the peritoneal cavity is opened, ascitic fluid, if present, should be evacuated. In some centers, fluid is submitted for *in vitro* research studies, such as molecular analyses. In cases of massive ascites, careful attention must be given to hemodynamic monitoring, especially for patients with borderline cardiovascular function.

The peritoneal cavity and retroperitoneum are thoroughly inspected and palpated to assess the extent of the primary tumor and the metastatic disease. All abdominal viscera must be palpated to exclude the possibility that the ovarian disease is metastatic, particularly from the stomach, colon, or pancreas. If optimal status is not considered achievable, extensive bowel and urologic resections are not indicated, except to overcome a bowel obstruction. However, removal of the primary tumor and omental cake is usually both feasible and desirable.

Pelvic Tumor Resection

The essential principle of removal of the pelvic tumor is to use the retroperitoneal approach. To accomplish this, the retroperitoneum is entered laterally, along the surface of the psoas muscles, which avoids the iliac vessels and the ureters. The procedure is initiated by division of the round ligaments bilaterally if the uterus is present. The peritoneal incision is extended cephalad, lateral to the ovarian vessels within the infundibulopelvic ligament, and caudally toward the bladder. With careful dissection, the retroperitoneal space is explored, and the ureter and pelvic vessels are identified. The pararectal and paravesicular spaces are identified and developed as described in Chapter 34.

The peritoneum overlying the bladder is dissected to connect the peritoneal incisions anteriorly. The vesicouterine plane is identified, and with careful sharp dissection the bladder is mobilized from the anterior surface of the cervix. The ovarian vessels are isolated, doubly ligated, and divided.

Hysterectomy, which is often not a simple operation, is then performed. The ureters must be carefully displayed to avoid injury. During this procedure, the uterine vessels can be identified. The hysterectomy and resection of the contiguous tumor are completed by ligation of the uterine vessels and the remainder of the tissues within the cardinal ligaments.

Because epithelial ovarian cancers tend not to invade the lumina of the colon or bladder, it is usually feasible to resect pelvic tumors without having to resect portions of the lower colon or the urinary tract (167,168). Resection of a small portion of the bladder may be required and, if so, a cystotomy should be performed to assist in resection of the disease (168).

Intestinal Resection

The disease may involve focal areas of the small or large intestine, and resection should be performed if it would permit the removal of all or most of the abdominal metastases and the patient will be left with optimal disease at the end of the cytoreduction. Apart from the rectosigmoid colon, the most frequent sites of

intestinal metastasis are the terminal ileum, the cecum, and the transverse colon. Resection of one or more of these segments of bowel may be necessary (167,169).

If the disease surrounds the rectosigmoid colon and its mesentery, it may be necessary to remove that portion of the colon to clear the pelvic disease (Fig. 35.10) (167). After the pararectal space is identified in such patients, the proximal site of colonic involvement is

identified, the colon and its mesentery are divided, and the rectosigmoid is removed along with the uterus *en bloc*. A reanastomosis of the colon is performed.

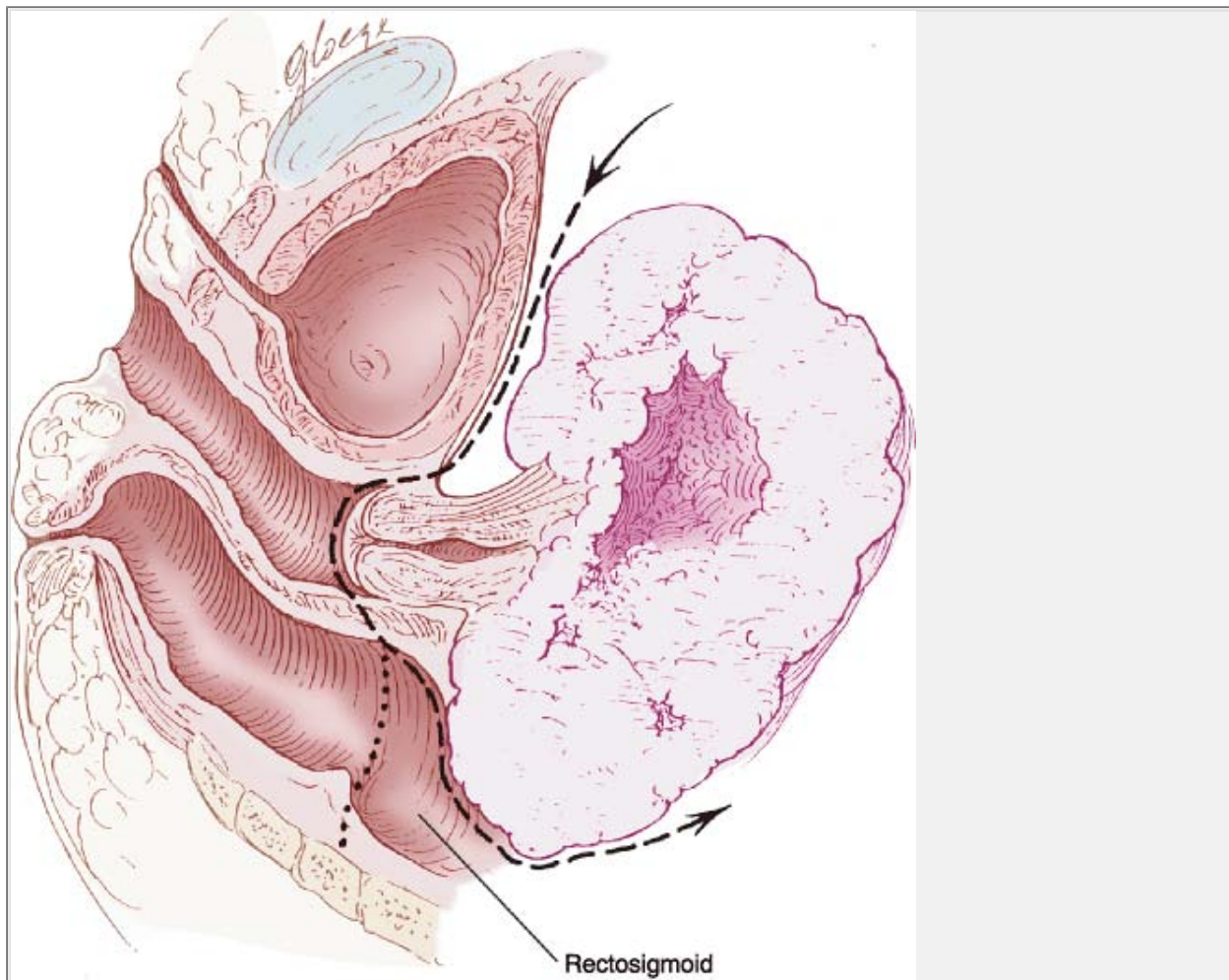
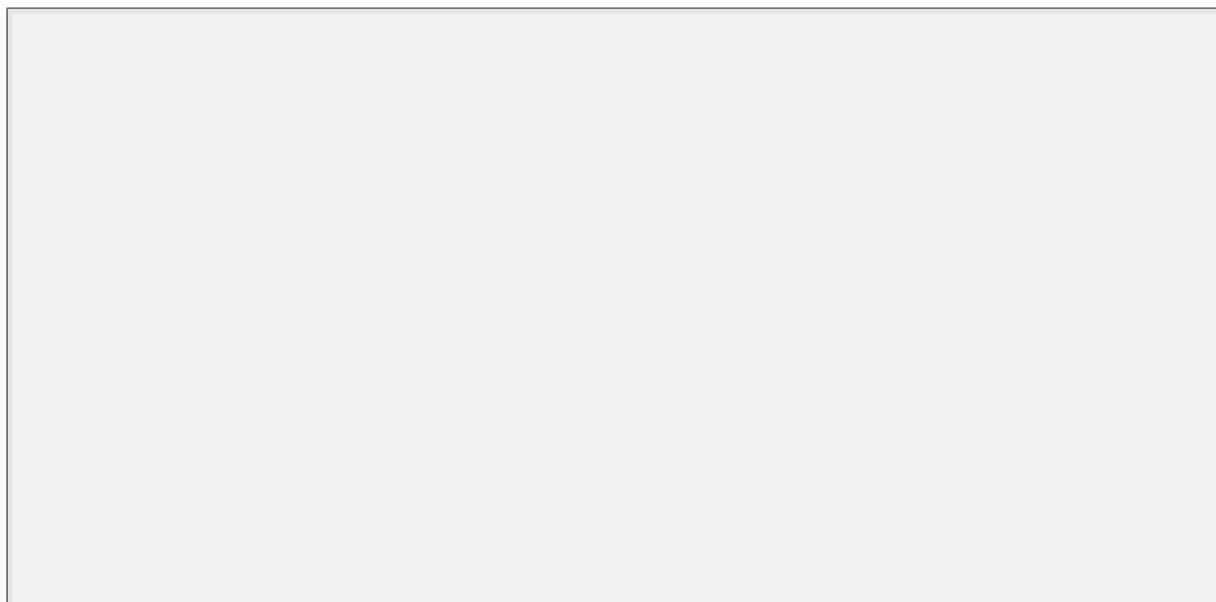


Figure 35.10 The resection of the pelvic tumor may include removal of the uterus, tubes, and ovaries, as well as portions of the lower intestinal tract. The *arrows* represent the plane of resection. (From **Berek JS, Hacker NF.** *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:465, with permission.)

Omentectomy

Advanced epithelial ovarian cancer often completely replaces the omentum, forming an "omental cake." This disease may be adherent to the parietal peritoneum of the anterior abdominal wall, making entry into the abdominal cavity difficult. After freeing the omentum from any adhesions to parietal peritoneum, adherent loops of small intestine are freed by sharp dissection. The omentum is then lifted and pulled gently in the cranial direction, exposing the attachment of the infracolic omentum to the transverse colon. The peritoneum is incised to open the appropriate plane, which is developed by sharp dissection along the serosa of the transverse colon. Small vessels are ligated with hemoclips. The omentum is then separated from the greater curvature of the stomach by ligation of the right and left gastroepiploic arteries and ligation of the short gastric arteries (Fig. 35.11).

The disease in the gastrocolic ligament can extend to the hilus of the spleen and splenic flexure of the colon on the left and to the capsule of the liver and the hepatic flexure of the colon on the right. Usually, the disease does not invade the parenchyma of the liver or spleen, and a plane can be found between the tumor and these organs. However, it will occasionally be necessary to perform splenectomy to remove all the omental disease (170).



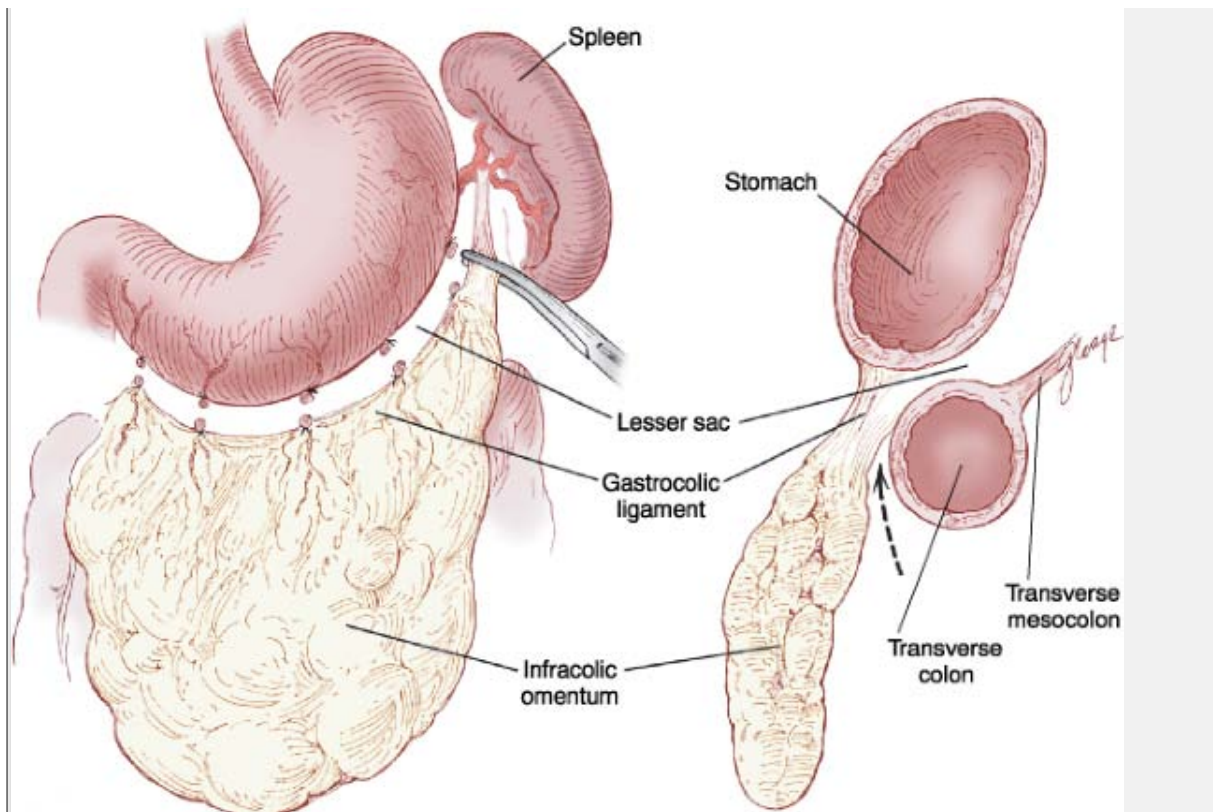


Figure 35.11 Separation of the omentum from stomach and transverse colon. *Arrow, the direction of the initial surgical approach.* (From **Heintz APM, Berek JS.** *Cytoreductive surgery for ovarian carcinoma.* In: **Piver MS,** ed. *Ovarian malignancies.* Edinburgh, UK: Churchill Livingstone, 1987: 134, with permission.)

Resection of Other Metastases

Other large masses of tumor that are located on the parietal peritoneum should be removed, particularly if they are isolated masses and their removal will permit optimal cytoreduction. Resection of extensive disease from the surfaces of the diaphragm is generally neither practical nor feasible, although solitary metastases may be resected, the diaphragm sutured, and a chest tube placed for a few days (170,171). The use of the Cavitron Ultrasonic Surgical Aspirator (CUSA) and the argon beam coagulator may help facilitate resection of small tumor nodules, especially those on flat surfaces (172,173).

Feasibility and Outcome

Although no randomized prospective study has ever been performed to define the value of primary cytoreductive surgery, all retrospective studies indicate that the diameter of the largest residual tumor nodule before the initiation of chemotherapy is significantly related to progression-free survival in patients with advanced ovarian cancer (176). In addition, quality of life is likely to be significantly enhanced by removal of bulky tumor masses from the pelvis and upper abdomen (179).

An analysis of the retrospective data available suggests that these operations are feasible for 70% to 90% of patients when performed by gynecologic oncologists (165,166). Major morbidity is in the range of 5% and operative mortality is in the range of 1% (169,174,175). Intestinal resection in these patients does not appear to increase the overall morbidity caused by the operation (169).

In a meta-analysis of 81 studies of women who underwent cytoreductive surgery for advanced ovarian cancer, Bristow et al. documented that the extent of debulking correlated with incremental benefits in survival, i.e., the greater the percentage of

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tumor reduction, the longer the survival: Each 10% increase in cytoreduction equaled a 5.5% increase in median survival (176). **Women whose cytoreduction was greater than 75% of their tumor burden had a median survival of 33.9 months compared with 22.7 months for women whose tumors were cytoreduced to less than 75%** ($p < 0.001$). The performance of a pelvic and para-aortic lymphadenectomy in patients with stage III disease does not prolong survival based on the results of a large prospective, randomized trial (177).

A prospective randomized study of "interval" cytoreductive surgery was carried out by the European Organization for the Research and Treatment of Cancer (EORTC).

Interval surgery was performed after three cycles of platinum-combination chemotherapy in patients whose primary attempt at cytoreduction was suboptimal. Patients in the surgical arm of the study demonstrated a survival benefit when compared with those who did not undergo interval debulking (178). Most of these patients had not had an aggressive attempt to debulk their tumor at their initial surgery. The risk of mortality was reduced by more than 40% in the group that was randomized to the debulking arm of the study. Based on these data, **the performance of a debulking operation as early as possible in the course of the patient's treatment should be considered the standard of care** (179).

A prospective phase III study of interval cytoreductive surgery was conducted by the GOG (180), but the study design was different because the patients entered on the trial had already undergone a maximal attempt at tumor resection at their initial surgery. The randomized findings showed no difference between the group who had an additional attempt at debulking after three cycles of chemotherapy compared with those who did not. The median survival of the 216 women who underwent interval cytoreduction was 32 months compared with 33 months for the 209 women who did not undergo surgical cytoreduction.

There is evidence that the survival of women with advanced ovarian cancer is improved when the surgeon is specifically trained to perform cytoreductive surgery (181,182,183,184) and when there is centralization of care (182). Therefore, **whenever feasible, patients with advanced ovarian malignancy should be referred to a subspecialty unit for primary surgery, and every effort should be made to attain as complete a cytoreduction as possible.**

Chemotherapy

Stage I Epithelial Ovarian Cancer

Early-stage, Low-risk

Guthrie et al. (152) studied the outcome of 656 patients with early-stage epithelial ovarian cancer. No patients who had stage Ia, grade 1 cancer who did not receive radiation or chemotherapy died of their disease; thus, adjuvant therapy is unnecessary. Furthermore, the GOG carried out a prospective, randomized trial of observation versus *melphalan* for patients with stage Ia and Ib, grades 1 and 2 disease (100). **Five-year survival for each group was 94% and 96%, respectively, confirming that adjuvant treatment did not improve survival. Therefore, no adjuvant chemotherapy is recommended for these patients.**

Early-stage, High-risk

In patients whose disease is high-risk, e.g., more poorly differentiated or in whom there are malignant cells either in ascitic fluid or in peritoneal washings, additional therapy is indicated. Most investigators recommend chemotherapy for these patients

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(185,186,187,188,189,190,191,192,193,194,195,196,197,198). Chemotherapy for patients with early-stage high-risk epithelial ovarian cancer can be either single agent or multiagent. Some researchers have questioned the wisdom of overly aggressive chemotherapy in women with early-stage disease, suggesting that the evidence for a durable impact on survival is marginal (187,188,194). Furthermore, the risk of leukemia with alkylating agents and platinum make the administration of adjuvant therapy risky unless there is a significant benefit (199,200).

Because *cisplatin*, *carboplatin*, *cyclophosphamide*, and *paclitaxel (Taxol)* are active single agents against epithelial ovarian cancer, these drugs have been administered in various combinations. There are some series in which *cisplatin* or *cyclophosphamide* (PC) or both have been used to treat patients with stage I disease (189,190,191). In a GOG trial of

three cycles of *cisplatin* and *cyclophosphamide* versus intraperitoneal chromic phosphate (³²P) in patients with stage Ib and Ic disease, the progression-free survival of women receiving the *platinum*-based chemotherapy was 31% higher than those receiving the radiocolloid (191). Similar results were also reported by a multicenter trial performed in Italy by the Gruppo Italiano Collaborativo Oncologica Ginecologica (GICOG) for progression-free survival, although there was no overall survival advantage. *Carboplatin* can be substituted for *cisplatin* in the therapy of these patients (197), although it is unclear if there is a survival benefit.

Two large parallel randomized phase III clinical trials were conducted on women with early-stage disease: the **International Collaborative Ovarian Neoplasm Trial 1 (ICON1)** and the **Adjuvant Chemotherapy Trial in Ovarian Neoplasia (ACTION)** (201,202).

In the ICON1 trial, 477 patients from 84 centers in Europe were entered. Patients of all stages were eligible for the trial if, in the opinion of the investigator, it was unclear whether adjuvant therapy would be of benefit. Most patients were said to have stages I and IIa disease but optimal **surgical staging was not required**, so it is likely an unquantified number of these women had stage III disease. Adjuvant platinum-based chemotherapy was given to 241 patients, and no adjuvant chemotherapy was given to 236 patients. **The 5-year survival was 73% in the group who received adjuvant chemotherapy compared with 62% in the control group** (HR=0.65, $p=0.01$) (202).

In the ACTION trial, **440 patients from 40 European centers were randomized; 224 patients received adjuvant platinum-based chemotherapy, and 224 patients did not** (201). **Patients with stages I and IIa, grades 2 and 3 were eligible. Only** about one third of the total group was optimally staged (**151 patients**). **In the observation arm, optimal staging was associated with a better survival [hazard ratio (HR) = 2.31, $p = 0.03$], and in the nonoptimally staged patients, adjuvant chemotherapy was associated with an improvement in survival (HR = 1.78, $p = 0.009$).** In optimally staged patients, no benefit of adjuvant chemotherapy was seen. **Therefore, in the ACTION trial, the benefit from adjuvant chemotherapy was limited to the patients with nonoptimal staging, suggesting that patients might only benefit if they had a higher likelihood of occult microscopic dissemination.**

When the data from the two trials were combined and analyzed (203), a total of 465 patients were randomized to receive platinum-based adjuvant chemotherapy and 460 to observation until disease progression. After a median follow-up of more than 4 years, the overall survival was 82% in the chemotherapy arm and 74% in the observation arm (HR = 0.67, $p = 0.001$). Recurrence-free survival was also better in the chemotherapy arm: 76% versus 65% (HR = 0.64, $p = 0.001$). The results of this analysis must be interpreted with caution, because most of the patients did not undergo thorough surgical staging, but **the findings suggest that platinum-based chemotherapy should be given to patients who have not been optimally staged.**

The current GOG trial includes patients with high-risk stage I and stage II disease, and consists

observation versus 26 weeks of weekly low-dose (40 mg/m²) *paclitaxel*. High-risk stage I is defined as stages Ia or Ib, grade 3, stage Ic, or clear cell carcinomas.

The recommendations for therapy follow:

- **Patients with high-grade, high-risk stage I epithelial ovarian cancer should be given adjuvant chemotherapy. The type depends on the patient's overall health and status.**
- **Treatment with *carboplatin* and *paclitaxel* chemotherapy for three to six cycles seems desirable in these patients, whereas a short course of a single agent, either *carboplatin* or *paclitaxel*, may be preferable for older women.**

Advanced-stage Epithelial Ovarian Cancer

Systemic multiagent chemotherapy is the standard treatment for metastatic epithelial ovarian cancer (204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222). After the introduction of *cisplatin* in the latter half of the 1970s, platinum-based combination chemotherapy became the most frequently used treatment regimen in the United States. *Paclitaxel* became available in the 1980s, and this drug was incorporated into the combination chemotherapy in the 1990s (204,205,206,207,208,209). Comparative trials of *paclitaxel*, *cisplatin*, and *carboplatin* are summarized below.

In a meta-analysis performed on studies of patients with advanced-stage disease, those patients given *cisplatin*-containing combination chemotherapy were compared with those treated with regimens that did not include *cisplatin* (213). Survival differences between the groups were seen from 2 to 5 years, with the *cisplatin* group having a slight survival advantage, but this difference disappeared by 8 years.

The major advance in the treatment of advanced-stage disease was the incorporation of *paclitaxel* into the chemotherapeutic regimens. A series of randomized, prospective clinical trials with *paclitaxel*-containing arms have defined the current recommended treatment protocol in advanced epithelial ovarian cancer (207,208,217,218).

Reporting the GOG data (Protocol 111), McGuire et al. showed that the combination of *cisplatin* (75 mg/m²) and *paclitaxel* (135 mg/m²) was superior to *cisplatin* (75 mg/m²) and *cyclophosphamide* (600 mg/m²), each given for six cycles (207). In suboptimally resected patients, the *paclitaxel*-containing arm produced a 36% reduction in mortality. These data were verified in a trial conducted jointly by the European Organization for the Research

and Treatment of Cancer (EORTC), the Nordic Ovarian Cancer Study Group (NOCOVA), and the National Cancer Institute of Canada (NCIC), in which patients with both optimal and suboptimal disease were treated (208). In this study, the *paclitaxel*-containing arm produced a significant improvement in both progression-free interval and overall survival in both optimal and suboptimal groups. **Based on these two studies, *paclitaxel* should be included in the primary treatment of all women with advanced-stage epithelial ovarian cancer, unless precluded by toxicity.**

A three-arm comparison of *paclitaxel* (T) versus *cisplatin* (P) versus PT in suboptimal stage III and IV patients (Protocol 132) showed equivalency in the three groups, but crossover from one drug to the other was permitted (209). The study essentially showed that the combination regimen was better tolerated than the sequential administration of the agents in suboptimally resected patients.

There is no evidence that increasing the dose of *cisplatin* >50 mg/m² improves survival (221,222,223).

The second-generation platinum analogue, *carboplatin*, was introduced and developed to have less toxicity than its parent compound, *cisplatin*. In early trials, *carboplatin* was shown to have lower overall toxicity (211). Fewer gastrointestinal side effects, especially

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nausea and vomiting, were observed than with *cisplatin*, and there was less nephrotoxicity, neurotoxicity, and ototoxicity. *Carboplatin* is, however, associated with a higher degree of myelosuppression.

The initial studies showed that *carboplatin* and *cisplatin* had approximately a 4:1 equivalency ratio. Thus, a standard single-agent dose of about 400 mg/m² has been used in most phase II trials (217,218,219). **The dose is calculated by using the area under the curve (AUC) and the glomerular filtration rate (GFR) according to the Calvert formula (223). The target AUC is 5 to 6 for untreated patients with ovarian cancer. Alternatively, a dose of approximately 350 to 450 mg/m² *carboplatin* can be used initially in patients with a normal serum creatinine and adjusted to toxicity.** A platelet nadir of approximately 50,000/mL is a suitable target (211).

Carboplatin and Paclitaxel

Two randomized, prospective clinical studies have compared the combination of *paclitaxel* and *carboplatin* to *paclitaxel* and *cisplatin* (217,218). In both studies, the efficacy and survivals were similar, but the toxicity was more acceptable with the *carboplatin*-containing regimen. In the first trial, GOG Protocol 158, the randomization was *carboplatin* AUC=7.5 and *paclitaxel* 175 mg/m² over 3 hours versus *cisplatin* 75 mg/m² and *paclitaxel* 135 mg/m² over 24 hours (Fig. 35.12). The disease progression-free survival of the *carboplatin*-containing arm was 22 months versus 21.7 months for the control arm (217). The gastrointestinal and neurotoxicity

of the *carboplatin* arm were appreciably lower than that of the *cisplatin* arm. A similar result was obtained in a large randomized trial in Germany (218), in which the dose of *carboplatin* was AUC = 6 and *paclitaxel* was 185 mg/m² over 3 hours compared with the same dose of *paclitaxel* and *cisplatin* 75 mg/m². Based on these data, **the preferred regimen in patients with advanced-stage disease has been the *paclitaxel* plus *carboplatin* combination** (219).

The International Collaborative Ovarian Neoplasm (ICON) 3 trial was a study of 2,074 women with all stages of ovarian cancer, including 20% who had stage I or II disease (224). ***Carboplatin* plus *paclitaxel* was compared with two non-*paclitaxel* regimens, *carboplatin* (70%), or CAP (30%).** The regimens were chosen before randomization and based on the clinical preference of the treating physician. One third of patients who received *carboplatin* or CAP subsequently received second-line *paclitaxel*, and this additional chemotherapy was often given before clinical progression. With a median follow-up of 51 months, the *carboplatin* plus *paclitaxel* and the control groups had a similar progression-free survival (0.93) and overall survival (0.98). **The median survival for the *paclitaxel* plus *carboplatin* and control groups was 36.1 and 35.4 months, respectively.** The median duration of progression-free survival was 17.3 and 16.1 months, respectively. **The researchers concluded that single agent *carboplatin* and CAP were as effective as *paclitaxel* and *carboplatin* for first-line chemotherapy.** Because *carboplatin* as a single agent had a lower toxicity than the other regimens and the median survival (33 months) was similar in the prior trial (ICON 2) that had compared *carboplatin* and CAP as first-line treatment (225), the researchers suggested that *carboplatin* alone was the preferred therapy. **However, the design of the study limits the validity of the results, because patients with FIGO stage I to IV disease were included, the extent of primary surgery was variable, and the study was not audited by an independent data monitoring committee. Also, the majority (85%) of patients who relapsed after single-agent *carboplatin* or *paclitaxel* subsequently received the other drug. Therefore, the study is not conclusive.**

Carboplatin and Docetaxel

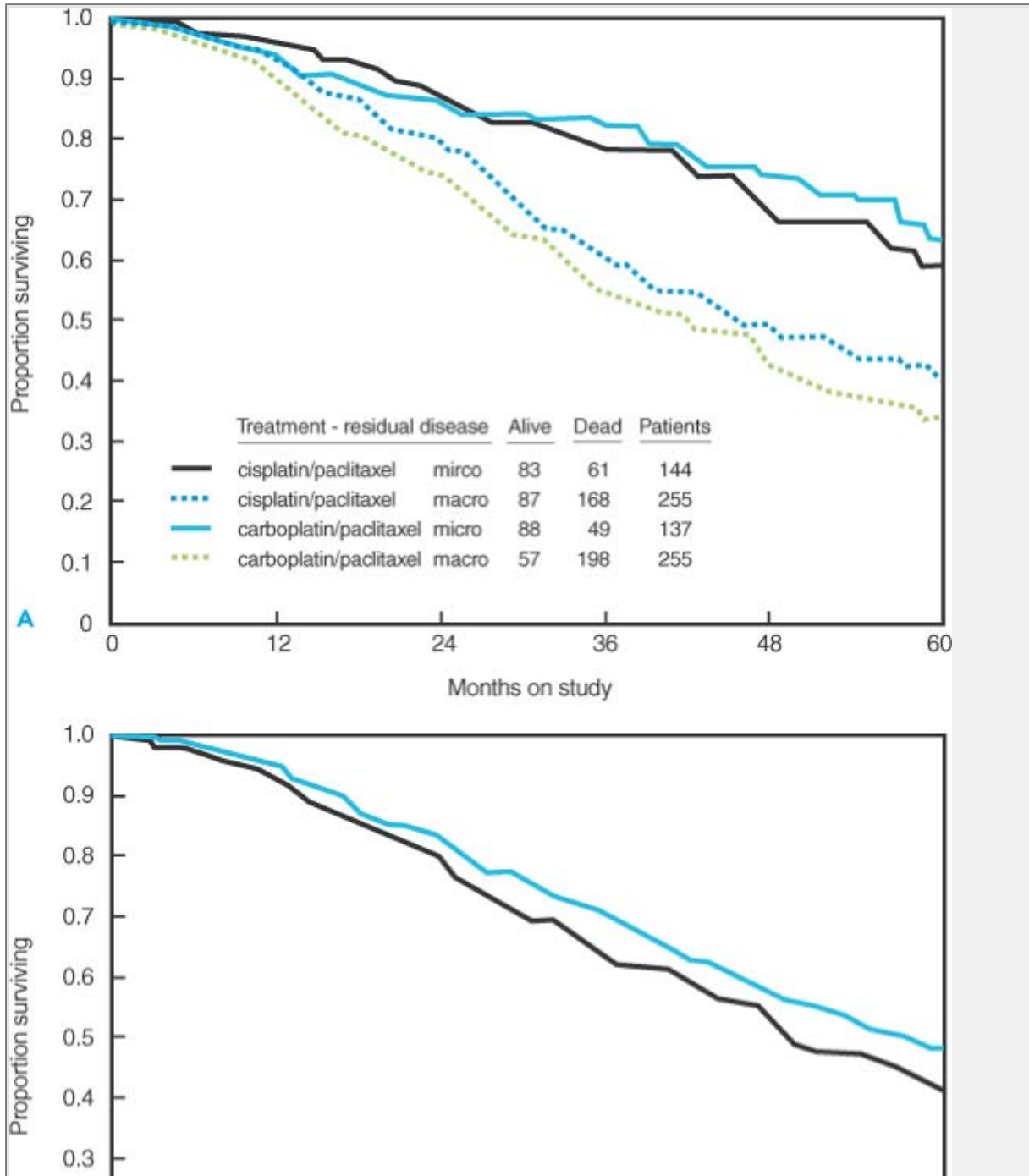
Docetaxel has a different toxicity profile from *paclitaxel*. The SCOT-ROC (Scottish Gynaecological Cancer Trials Group) study randomly assigned 1,077 women with stage Ic

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to IV epithelial ovarian cancer to *carboplatin* with either *paclitaxel* or *docetaxel* (226). **The efficacy of *docetaxel* appeared to be similar to *paclitaxel*:** The median progression-free survival was 15.1 months versus 15.4 months, and **the *docetaxel* group had fewer neurologic effects, arthralgias, myalgias, and extremity weakness than the *paclitaxel* group.** However, the *docetaxel* plus *carboplatin* regimen was associated with significantly more myelosuppression and its consequences, i.e., serious infections

and prolonged grade 3 to 4 neutropenia. Therefore, additional study will be necessary to determine whether *docetaxel* should supplant *paclitaxel* in the primary treatment of epithelial ovarian cancer.



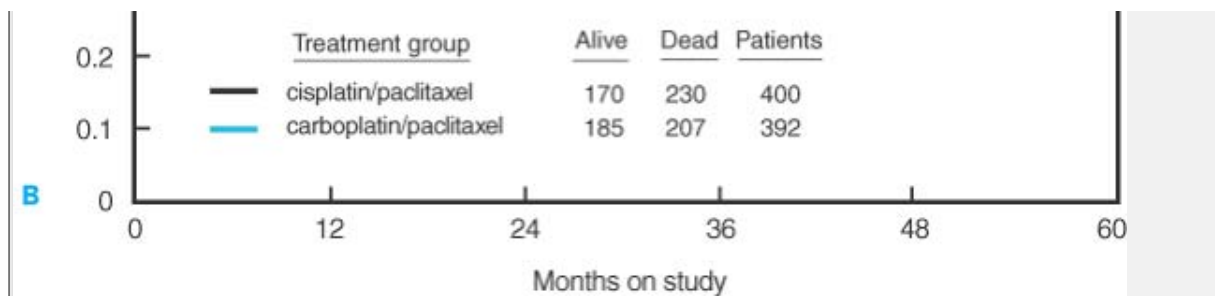


Figure 35.12 Survival of patients with stage III epithelial ovarian cancer treated with carboplatin and paclitaxel versus cisplatin and paclitaxel: a Gynecologic Oncology Group study. A: Survival by treatment. **B:** Survival by treatment group (micro vs. macro). (From **Ozols RF, Bundy BN, Greer BE, et al.** Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2003;21:3194–3200, with permission). (From **Berek JS, Hacker NF.** *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005: 477, with permission.)

Five-Arm Trial

An intergroup, international trial (GOG 182/SWOG 182/ICON 5) compared the standard combination of *carboplatin* and *paclitaxel* with these drugs in combination with *gemcitabine*, *topotecan*, or *liposomal doxorubicin* in sequential doublets or triplets (227,228). The study shows that the addition of any three drugs to the standard chemotherapy does not enhance outcome or survival (228).

Intraperitoneal Chemotherapy

A randomized, prospective GOG study (Protocol 104) of intraperitoneal *cisplatin* versus intravenous *cisplatin* (100 mg/m²), each given with 750 mg/m² *cyclophosphamide*, has been performed jointly by the Southwest Oncology Group (SWOG) and the GOG in patients with minimal residual disease (229). **The intraperitoneal *cisplatin* arm had a somewhat longer overall median survival than the intravenous arm, 49 versus 41 months ($p = 0.03$).** In the patients with minimal residual disease (< 0.5 cm maximal residual), however, there was no difference between the two treatments, 51 versus 46 months ($p = 0.08$).

In a follow-up GOG study (Protocol 114), the dose-intense arm was initiated by giving a moderately high dose of *carboplatin* (dose AUC = 9) for two induction cycles, followed by intraperitoneal *cisplatin* 100 mg/m² and intravenous *paclitaxel* 135 mg/m² over 24 hours, versus intravenous *cisplatin* 75 mg/m² and intravenous *paclitaxel* 135 mg/m² (230). The dose-intense arm results were slightly better—the disease progression-free median survival was 27.6 months compared with 22.5 months for the control arm ($p = 0.02$). However, there was

no difference in overall survival (52.9 months versus 47.6 months, $p = 0.056$). Thus, based on this study, it was unclear if dose intensification with intraperitoneal *cisplatin* would have a sustained long-term impact on the survival of these patients.

A third randomized prospective GOG study (Protocol 172) compared intraperitoneal *cisplatin* and *paclitaxel* versus intravenous *cisplatin* and *paclitaxel* (231). The combination of *cisplatin* 75 mg/m² and *paclitaxel* 135 mg/m² given intravenously every 3 weeks was compared with *paclitaxel* 135 mg/m² intravenous day 1, followed by *cisplatin* 100 mg/m² intraperitoneal day 2, and *paclitaxel* 60 mg/m² intraperitoneal day 8 every 3 weeks, each given for 6 cycles. **While 83% of the patients randomized to intravenous chemotherapy completed all 6 cycles of therapy, only 42% of those treated with intraperitoneal chemotherapy completed the 6 cycles, principally because of catheter-related complications. For patients in either group who could not complete the therapy because of *cisplatin*-related toxicity, the chemotherapy was switched to intravenous *carboplatin*.** Comparing the intravenous and intraperitoneal arms, the median duration of progression-free survival was 18.3 and 23.8 months, respectively ($p = 0.05$). **The median duration of overall survival in the intravenous-therapy and intraperitoneal-therapy groups was 49.7 and 65.6 months, respectively ($p = 0.03$)** (231). Quality of life was significantly worse in the intraperitoneal-therapy group before cycle 4 and 3-6 weeks after treatment but not one year after treatment. A summary of the intraperitoneal catheter related issues in this trial has been presented (232).

Based on these randomized trials, the intraperitoneal route of administration for *cisplatin* and *paclitaxel* chemotherapy in the primary treatment of optimally resected

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stage III ovarian cancer is an acceptable therapeutic alternative to intravenous chemotherapy with *carboplatin* and *paclitaxel* (233). **However, thus far there has been no randomized direct comparison of this intraperitoneal regimen to intravenous *carboplatin* and *paclitaxel* or to intraperitoneal *carboplatin* and *paclitaxel*. Intraperitoneal therapy can be used in patients with optimally resected tumors who have a good performance status and are in overall good health. Because intraperitoneal chemotherapy is more cumbersome and has a higher morbidity than intravenous therapy, the use of this technique of drug delivery should be individualized after thorough discussion with the patient.**

Neoadjuvant Chemotherapy

Some authors have suggested that, for patients with suboptimal stage III and stage IV disease, chemotherapy may be given in lieu of debulking surgery. A series performed by Schwartz et al. (234) suggested that the survival of these patients treated with neoadjuvant or cytoreductive chemotherapy was comparable to those patients historically treated in the same institution with debulking surgery followed by conventional chemotherapy. As other

authors have shown a benefit to debulking patients before chemotherapy (235,236), the issue would need to be resolved by a prospective clinical trial. However, two or three cycles of chemotherapy before cytoreductive surgery may be helpful in patients with massive ascites and large pleural effusions. The chemotherapy may dry up the effusions, improve the patient's performance status, and decrease postoperative morbidity, particularly chest morbidity.

Chemotherapeutic Recommendation in Advanced Epithelial Ovarian Cancer

For the treatment of advanced-stage epithelial ovarian cancer, the following is recommended (Table 35.4):

- **Combination chemotherapy with intraperitoneal *cisplatin* and *paclitaxel* or intravenous *carboplatin* and *paclitaxel* are the treatments of choice for patients with advanced disease. The advantages and disadvantages of the intraperitoneal versus intravenous routes of administration of these drugs should be discussed with the patient.**
- **The recommended doses and schedule for intraperitoneal chemotherapy are *paclitaxel* 135 mg/m² intravenous on day 1, followed by *cisplatin* 50-100 mg/m² intraperitoneal on day 2, followed by *paclitaxel* 60 mg/m² intraperitoneal on day 8, every 3 weeks for 6 cycles, as tolerated.**
- **The recommended doses and schedule for intravenous chemotherapy are: *carboplatin* (starting dose AUC = 5-6), and *paclitaxel* (175 mg/m²), every 3 weeks for 6-8 cycles.**
- **In patients who cannot tolerate combination chemotherapy, single-agent, intravenously administered *carboplatin* (AUC = 5-6) or *paclitaxel* 175 mg/m² can be given.**
- **In patients who have a hypersensitivity to *paclitaxel* or *carboplatin*, either desensitization can be performed, or an alternative active drug can be substituted (e. g., *docetaxel*, *liposomal doxorubicin*, *topotecan*, *etoposide*). *Etoposide* can be given orally.**

The treatment of all patients with advanced-stage disease is approached in a similar manner, with modifications based on the overall status and general health of

the patient, as well as the extent of residual disease present at the time treatment is initiated.

Table 35.4. Combination Chemotherapy for Advanced Epithelial Ovarian Cancer: Recommended Regimens				
Drugs	Dose (mg/m ²)*	Route	Interval (weeks)	Treatments (cycles)
Standard regimens				
Intraperitoneal chemotherapy				
<i>Paclitaxel</i>	135	IV	3, day 1	6
<i>Cisplatin</i>	50–100	IP	day 2	
<i>Paclitaxel</i>	60	IP	day 8	
Intravenous chemotherapy				
<i>Paclitaxel</i>	175	IV	3	6–8
<i>Carboplatin</i>	*AUC = 5–6	IV		
<i>Paclitaxel</i>	135	IV	3	6–8
<i>Cisplatin</i>	75	IV		
Alternative drugs**				
<i>Docetaxel</i>	75	IV	3	
<i>Doxorubicin, liposomal</i>	35–50	IV	3–4	
<i>Topotecan</i>	1.0–1.25	IV	1	
	4.0	IV	3(daily ×3 3–5 days)	
<i>Etoposide</i>	50	PO	3, days 14–21	

* Except for *carboplatin* dosing, where AUC—area under the curve—dose calculated by using Calvert formula (223).

**Drugs that can be substituted for *paclitaxel* if hypersensitivity to that drug occurs; the number of treatments administered as tolerated.

Immunotherapy

There is currently a great deal of interest in the use of immunotherapies in ovarian cancer. Cytokines have been used extensively in second-line therapy, and the activity of *interferon- α* , *interferon- γ* and *interleukin-2* has been demonstrated, as discussed below (3). In a recent trial of *interferon- γ* plus *cisplatin* combination chemotherapy versus chemotherapy alone, patients who received the *interferon* had a longer disease progression-free survival (237). A randomized, multicenter trial of first-line *carboplatin* and *paclitaxel* with or without *interferon- γ* has been conducted, and there is no survival advantage in the patients who received *interferon- γ* .

Hormonal Therapy

There is no evidence that hormonal therapy alone is appropriate primary therapy for advanced ovarian cancer. **The use of progestational agents in the treatment of recurrent well-differentiated endometrioid carcinomas is supported by the current data.** In one study, 30 evaluable patients with recurrent epithelial cancers were treated; 17 (57%) had an objective response, and three (10%) of these patients achieved a complete response (238). All responding patients had well-differentiated, estrogen receptor—positive tumors. A trial of *tamoxifen* in combination with multiagent chemotherapy is being conducted.

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Consolidation and Maintenance of Complete Clinical Response to First-line Chemotherapy

Because as many as 80% of women with advanced-stage disease who completely respond to their first-line chemotherapy will ultimately relapse, several trials have been conducted that administer a drug to these patients immediately following their primary treatment in an effort to decrease the relapse rate.

Paclitaxel

In a study conducted by the GOG and SWOG, 277 women with advanced ovarian cancer who had a complete clinical remission to first-line chemotherapy were randomized to receive 3 or 12 cycles of additional single-agent *paclitaxel* (175 or 135 mg/m² every 28 days) (239). Patients were excluded if they had developed grade 2 or 3 neurotoxicity during their initial chemotherapy. Because of cumulative toxicity, the mean number of actual cycles of *paclitaxel* received by the group assigned to receive 12 cycles was 9. The treatment-related grade 2 to 3 neuropathy was more common with longer treatment, 24% versus 14% of patients, respectively. **The study was closed after a median follow-up of only 8.5 months, and an interim analysis showed a significant 7-month prolongation in median progression-free survival (28 versus 21 months) with 9 versus 3 months of consolidation *paclitaxel*. However, there was no difference in median overall survival.** The rate of disease progression increased significantly after maintenance therapy was discontinued, which suggested that long-term survival would not be likely to be improved. Furthermore, it is unlikely that a survival benefit will be seen with longer follow-up, because patients assigned to three cycles were given the option of receiving an additional nine courses of *paclitaxel* after the study was discontinued (240). Another placebo-controlled, randomized trial using two formulations of *paclitaxel* is being conducted by the GOG.

Topotecan

Four additional treatment courses of *topotecan* were administered to patients following six cycles of *carboplatin* and *paclitaxel* in two randomized trials, one conducted in Italy (241) and the other in Germany (242). In the larger trial conducted in Germany, 1,059 evaluable patients were randomly assigned to six cycles of *paclitaxel* (175 mg/m² over 3 hours) and *carboplatin* (AUC 5) with (537 patients) or without (522 patients) four additional cycles of *topotecan* (1.25 mg/m² IV days 1 to 5 every 3 weeks) (242). In the Italian trial, 273 women were randomly assigned to receive four additional cycles (137 patients) of *topotecan* at a dose of 1 mg/m² on days 1 to 5 every 3 weeks or no further chemotherapy (136 patients) (241). **Preliminary reports suggest no significant differences in either progression-free or overall survival in patients who received four to six cycles of consolidation *topotecan*.**

Cisplatin

In a randomized clinical trial of intraperitoneal *cisplatin* for consolidation versus observation, there was no difference in survival between the treatment arms (243).

Immunotherapy

Trials of monoclonal antibodies directed toward ovarian cancer-associated antigens are being conducted. Monoclonal antibodies (MonAb) directed toward CA125 (OvaRex) (244) and toward the HMFG (human milk fat globulin) (245) tumor-associated antigens have been conducted. In a randomized, placebo-controlled trial of intravenous OvaRex (ant-CA125 MonAb) as consolidation/maintenance, Berek et al. reported that a subset of patients with optimal ovarian cancer who had achieved a prompt clinical remission after three cycles of chemotherapy (as indicated by a rapid decline in CA125) had a longer time to disease relapse (24 months) compared with those who received placebo (10.8 months) ($p = 0.06$) (244). A randomized trial of an intraperitoneally administered yttrium-labeled antimucin (HMFG) MonAb versus placebo was not associated with an improved overall survival after a negative second-look laparoscopy (245). However, the time to intraperitoneal relapse was effectively delayed by the IP MonAb, suggesting regional activity for the drug.

Summary

The clinical benefit of consolidation and maintenance chemotherapy and immunotherapy remains unclear. Patients and their physicians may consider prolonged single-agent *paclitaxel* an option, but it should not be considered the standard of care at this time.

Treatment Assessment

Many patients who undergo optimal cytoreductive surgery and subsequent

chemotherapy for epithelial ovarian cancer will have no evidence of disease at the completion of treatment. Tumor markers and radiologic assessments have proven to be too insensitive to exclude the presence of subclinical disease. Therefore, a second-look surgery has been performed to evaluate these patients (142,246,247,248,249,250,251,252,253,254,255). Most often, patients have undergone formal reassessment laparotomy, although the laparoscope has also been used in this circumstance (253,254,255). However, there is a 35% false-negative rate if laparoscopy is used for a second-look procedure (142,254).

Tumor Markers

Tumor markers are not reliable enough to predict accurately which patients with epithelial tumors will experience complete eradication of disease with a particular therapy. Carcinoembryonic antigen (CEA) levels are often elevated in patients with ovarian cancer, but the test is too nonspecific and insensitive to have much use in the management of these patients (42). The level of CA125, a surface glycoprotein associated with müllerian epithelial tissues, is elevated in about 80% of patients with epithelial ovarian cancers, particularly those with nonmucinous tumors. The levels frequently become undetectable after the initial surgical resection and one or two cycles of chemotherapy.

Levels of CA125 have been correlated with findings at second-look operations. Positive levels are useful in predicting the presence of disease, but negative levels are an insensitive determinant of the absence of disease. In a prospective study (256), the predictive value of a positive test was shown to be 100%; if the level of CA125 was positive (>35 U/mL), disease was always detectable in patients at the second-look procedure. The predictive value of a negative test was only 56%; if the level was <35 U/mL, disease was present in 44% of the patients at the time of the second-look surgery. **A review of the literature suggests that an elevated CA125 level predicts persistent disease at second-look surgery in 97% of the cases (257), but the CA125 level is not sensitive enough to exclude subclinical disease in many patients.**

Serum CA125 levels can be used during chemotherapy to follow those patients whose levels were positive at the initiation of therapy (3,257). The change in level generally correlates with response. Those patients with persistently elevated levels after three cycles of treatment most likely have persistent disease. When levels rise after treatment, almost invariably treatment has failed, and continuation of the current regimen is futile. A retrospective study has determined that a doubling of the CA125 level from its nadir in those patients with a persistently elevated level accurately predicts disease progression (258).

Radiologic Assessment

For patients with stage I to III epithelial ovarian cancer, radiologic tests generally have been of limited value in assessing the response to therapy for subclinical

disease. Ascites can be readily detected, but even quite large omental metastases can be missed on CT scan (259). If liver enzyme levels are abnormal, the liver can be evaluated with a CT scan or ultrasonography. A positive CT scan and fine-needle aspiration (FNA) cytology indicating tumor persistence could document persistent or recurrent disease, but the false-negative rate of a CT scan is about 45% (260). **Positron-emission tomography (PET) alone or with CT imaging may help in the detection of relapse, although the relative value of adding PET has not been established. There appears to be a higher false-positive rate with PET compared**

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with CT (90,91,92). MRI can be used as an alternative to CT in patients with allergies to the contrast medium (90).

Second-look Operations

A second-look operation is one performed on a patient who has no clinical evidence of disease after a prescribed course of chemotherapy to determine the response to therapy.

Second-look Laparotomy

The technique of the second-look laparotomy is essentially identical to that for the staging laparotomy (142). The operation should be performed through a vertical abdominal incision. The incision should be initiated below the level of the umbilicus, so that if pelvic disease is detected in the absence of any palpable upper abdominal disease, a smaller incision might suffice. The incision can be extended cranially as needed. After multiple cytologic specimens have been obtained, samples of the peritoneal surfaces should be collected for biopsy, particularly in any areas of previously documented tumor. These are the most important areas to sample for biopsy because they are most likely to give a positive result. Any adhesions or surface irregularities should be sampled. In addition, biopsy specimens should be taken from the pelvic side walls, the pelvic cul-de-sac, the bladder, the paracolic gutters, the residual omentum, and the diaphragm. A pelvic and para-aortic lymph node dissection should be performed for those patients whose nodal tissues have not been previously removed.

About 30% of patients with no evidence of macroscopic disease will have microscopic metastases (246,247,248,249). Also, for many patients with microscopic disease, it will be detected in only the occasional biopsy or cytologic specimen. Therefore, a large number of specimens (at least 20 to 30) should be obtained to minimize possibility of false-negative results of the operation. **In selected patients in whom gross residual tumor is discovered at second-look surgery, resection of isolated masses may be performed.** The removal of all macroscopic areas of disease might facilitate response to salvage therapies (261,262,263,264,265,266,267,268).

Second-look laparotomies have not been shown to influence patient survival

(250,251). **Therefore, they should be performed selectively, e.g., in patients receiving therapy in a setting where second-line therapies are undergoing clinical trials.**

The findings at second-look correlate with subsequent outcome and survival (142,246,247,248,249,250,251,252). Patients who have no histologic evidence of disease have a significantly longer survival than those in whom microscopic or macroscopic disease is documented at laparotomy (251,252). The attainment of negative findings with second-look surgery is not tantamount to a cure (252). Indeed, the reported probability that a patient will have a recurrence after a negative second-look laparotomy ranges from 30% to 50% at 5 years (142,246,247,248,249,250,251,252). Clearly, it is not possible to sample every potential site of disease. In addition, disease can become clinically apparent in sites that are occult, such as the liver parenchyma (98). Most recurrences after a negative second-look laparotomy occur in patients with poorly differentiated cancers (252).

Variables associated with the outcome of the second-look laparotomy are (i) initial stage, (ii) tumor grade, (iii) the size of the residual tumor and the size of the largest metastatic tumor before treatment, and (iv) the type of chemotherapy. No single variable or combination of variables is sufficiently predictive of the findings of a second-look laparotomy (3,142).

Second-look Laparoscopy

The laparoscope in epithelial ovarian cancer patients may be used to stage disease in patients who have undergone a prior laparotomy for a tumor that was incompletely staged. Second-look laparoscopy may also be useful for patients on experimental treatment protocols, especially second-line treatments that require some evaluation of

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response. The advantage of laparoscopy is that it is a less invasive operation; the disadvantage is that visibility may be limited by the frequent presence of intraperitoneal adhesions (3,253,254,255). The development of newer techniques for retroperitoneal lymphadenectomy has potentially increased the utility of the endoscopic approach to second look.

Second-line Therapy

Secondary Cytoreduction

Secondary cytoreduction maybe defined as an attempt at cytoreductive surgery at some stage following completion of first-line chemotherapy (261). Patients with progressive disease on chemotherapy are not suitable candidates for secondary cytoreduction, but patients who are clinically free of disease and undergo second-look laparotomy may benefit if all macroscopic residual disease can be resected (262,263,264). Patients with recurrent disease are occasionally candidates for surgical excision of their disease. **Tumor resection under**

these circumstances should be restricted to those who have a disease-free interval of at least 12, but preferably 24, months or those in whom all macroscopic disease can be resected, regardless of the disease free interval (261,262,263,264,265,266,267,268).

Second-line Chemotherapy

If disease persists at the time of second-look laparotomy, or if clinically progressive disease develops during primary therapy, patients usually have been switched to an alternative treatment, often a second-line chemotherapy. The response rates for second-line chemotherapies have been 15% to 35% for most drugs tested by the oral or intravenous route

(269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292).

Active drugs that have been used as single agents include *cisplatin*, *carboplatin*, *paclitaxel*, *docetaxel* (*Taxotere*), *topotecan*, *gemcitabine*, *etoposide* (*VP-16*), *doxorubicin* (*Doxil*), *vinorelbine* (*Navelbine*), *ifosfamide*, *5-fluorouracil* with *leucovorin*, and *hexamethylmelamine*.

Single-agent drugs are sometimes used for second-line chemotherapy because of their relative ease of administration and low toxicity.

Platinum-sensitive Disease

Second-line therapies have been categorized by whether the patients responded to their initial platinum-based chemotherapy. Although this concept has been variously defined, platinum sensitivity has been related to a disease progression-free interval of at least 6 months. Response rates after retreatment with *cisplatin* have been shown to be higher in patients whose time to clinical relapse after prior response to *cisplatin* is longer than 6 months, especially when it is 12 to 24 months (271,272,273). **Thus, the concept of platinum sensitivity is a continuum: The longer the interval, the higher the probability of a secondary response to secondary platinum-based chemotherapy.** *Carboplatin* is active as a second-line agent in patients who have responded to prior *cisplatin* treatment, and response rates in these patients have been 20% to 30% (271). The concept of platinum sensitivity and *paclitaxel* sensitivity should influence the choice of second-line chemotherapy.

In patients who have platinum-or *paclitaxel*-sensitive tumors, retreatment with a platinum drug or *paclitaxel* is appropriate. Second-line responses to *paclitaxel*, *carboplatin*, and *cisplatin* in those patients who have responded previously to *cisplatin* have been observed in 20% to 25% of patients. Furthermore, the length of a prior response to platinum-based chemotherapy is highly predictive of the upper limit of the duration of response to a subsequent platinum treatment using the same or similar drugs (274).

There are studies that suggest that a platinum plus *paclitaxel* may be better for second-line therapy than platinum alone (293,294). In a series of 25 women who relapsed 6 months or

longer after first-line *carboplatin* and *paclitaxel*, retreatment with the same combination of drugs resulted in a response rate of 91% and a median progression-free interval of more

than 9 months (294). Others suggest that single-agent therapy (*cisplatin* or *carboplatin*) should be considered the standard of care for platinum-sensitive relapsing disease (295,296). **In most studies, there is a lack of survival advantage and greater toxicity with multiagent compared with single-agent regimens**, although the combination of *carboplatin* and *paclitaxel* is well tolerated (297).

The use of combination platinum plus *paclitaxel* chemotherapy versus a single-agent platinum was tested in two multinational randomized phase III trials (298) and a randomized phase II study (299). In a report of the ICON4 (298) and AGO-OVAR-2.2 (299) trials, 802 women with platinum-sensitive ovarian cancer who relapsed after being treatment-free for at least 6 to 12 months were randomized to platinum -based chemotherapy (72% *carboplatin* or *cisplatin* alone; 17% CAP; 4% *carboplatin* plus *cisplatin*; and 3% *cisplatin* plus *doxorubicin*) or *paclitaxel* plus platinum-based chemotherapy (80% *paclitaxel* plus *carboplatin*; 10% *paclitaxel* plus *cisplatin*; 5% *paclitaxel* plus both *carboplatin* and *cisplatin*; and 4% *paclitaxel* alone). The AGO-OVAR-2.2 trial did not accrue its planned number of patients. In both trials, a significant proportion of the patients had not received *paclitaxel* as part of their initial chemotherapeutic regimen. **Combining the trials for analysis, there was a significant survival advantage for the *paclitaxel*-containing therapy** (HR = 0.82) with a median follow up of 42 months. **The absolute 2-year survival advantage was 7% (57% vs. 50%), and there was a 5-month improvement in median survival (29 vs. 24 months)**. Progression-free survival was better with the *paclitaxel* regimen (HR = 0.76); there was a 10% difference in 1-year progression-free survival (50% vs. 40%) and a 3-month prolongation in median progression-free survival (13 vs. 10 months). The toxicities were comparable, except there was a significantly higher incidence of grade 2 to 4 neurologic effects (20% vs. 1%) and alopecia (86% vs. 25%) in the *paclitaxel* group. Conversely, myelosuppression was significantly greater with the non-*paclitaxel*-containing regimens. **These data support the slight advantage of a second-line regimen containing both *paclitaxel* and a platinum agent compared with platinum-based therapy alone, especially in patients who have not received *paclitaxel* in their primary chemotherapeutic regimen.**

Platinum-resistant and Refractory Disease

In *cisplatin*-refractory patients, response rates to second-line *carboplatin* are less than 10% (270,272). The management of women who have platinum-resistant disease requires the use of non—cross-resistant agents. Single-agent therapy is typically used, because combination regimens are associated with more toxicity without additional benefit. There are a variety of active drugs; *paclitaxel*, *docetaxel*, *topotecan*, *liposomal doxorubicin*, *gemcitabine*, *oral etoposide*, and *tamoxifen* are the most frequently used. Other active agents include *vinorelbine*, *ifosfamide*, and *leucovorin-modulated 5-fluorouracil*. These agents have resulted

in second-line response rates of about 8% to 28% in patients with platinum-resistant disease (275,276,277,278,279,280,281,282,283,284,285,286,287,289,290,291,292).

Some researchers have used these drugs to prolong the "platinum-free interval," hoping that their use will allow the tumor to become platinum sensitive during the interval use of non-cross-resistant agents. The rationale for this method is that the platinum-free interval is equivalent to the treatment-free interval, and before the availability of other active drugs, these two terms were synonymous. However, there are no data to support the hypothesis that the interposition of another drug can produce an increased platinum sensitivity as a result of a longer interval since the last platinum treatment.

Single-agent *paclitaxel* shows objective responses in 24% to 30% in phase II trials of women with platinum-resistant ovarian cancer (300,301,302,303,304,305,306).

Weekly *paclitaxel* is active, and the toxicity, especially myelosuppression, is less than with the every-3-weeks regimens. *Docetaxel* also has some activity in these patients (307,308,309).

Topotecan is an active second-line treatment for patients with platinum-sensitive and platinum-resistant disease

(310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325). **Weekly**

***topotecan* administered at a dose of**

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4 mg/m²/week for 3 weeks with a week off every month produced a response rate similar to the 5-day regimen with considerably less toxicity; therefore, this is now considered the regimen of choice for this agent (325). *Liposomal doxorubicin* (*Doxil* in the United States and *Caelyx* in Europe) has activity in platinum- and taxane-refractory disease (326,327,328). **The predominant severe toxicity of *liposomal doxorubicin* is the hand-foot syndrome, also known as *palmar-plantar erythrodysesthesia* or *acral erythema*.**

This morbidity is observed in 20% of patients who receive 50 mg/m² every 4 weeks (326).

There have been two randomized trials comparing *liposomal doxorubicin* with *topotecan*. In a study of 237 women who relapsed after receiving one platinum-containing regimen, 117 of whom (49.4%) had platinum-refractory disease (328), *liposomal doxorubicin* 50 mg/m² over 1 hour every 4 weeks was compared with *topotecan* 1.5 mg/m²/day for 5 days every 3 weeks.

The two treatments had a similar overall response rate (20% vs. 17%), time to progression (22 vs. 20 weeks), and median overall survival (66 vs. 56 weeks).

The myelotoxicity was significantly lower in the *liposomal doxorubicin*-treated patients than with those receiving *topotecan* with grade 3 or 4 neutropenia (12% vs. 71%) and grade 3 or 4 thrombocytopenia (1% vs. 35%). However, with more long term follow-up of these patients (329), the median survival was 62.7 weeks for those treated with *liposomal doxorubicin* and 59.7 weeks for *topotecan*-treated patients ($p = 0.05$). In the subset of patients with platinum-sensitive disease, the median survival was 107.9 weeks for those treated with *liposomal doxorubicin* versus 70.1 weeks for *topotecan*-treated patients ($p = 0.017$), suggesting a slight advantage of the *liposomal doxorubicin* in this second-line setting.

Gemcitabine has been associated with response rates of 20% to 50%, with 15% to 30% in patients who are platinum resistant (330,331,332,333,334). Oral *etoposide* should be considered one of the principal drugs to be used in patients with *paclitaxel*- and platinum-resistant disease (335,336). Other active agents include hexamethylmelamine (337,338), capecitabine (339), 5-fluorouracil and leukovorin (340), and ifosfamide with mesna (341).

Hormonal Therapy

Tamoxifen has been associated with response rates of 15% to 20% in well-differentiated carcinomas of the ovary (342,343,344,345,346,346). The gonadotropin-agonist *leuprolide acetate* (*Lupron*) has been shown to produce a response rate of 10% in one series (347). Trials combining *tamoxifen* and *leuprolide acetate*, and *tamoxifen* and combination chemotherapy are being conducted (348). Aromatase inhibitors, e.g., *letrozole*, *anastrozole*, and *exemestane*, which have been shown to have activity in metastatic breast cancer, are being studied in relapsed ovarian cancer (349). One of the principal advantages of this class of agents is the very low toxicity (350).

Immunotherapy

Herceptin, an antibody directed toward the extracellular protein produced when the HER-2/*neu* oncogene is overexpressed, has been used extensively in breast cancer, where it has been shown to improve the response rate to chemotherapy in selected patients. Trials of this antibody in patients whose ovarian cancers overexpress erbB2 was conducted by the GOG, but only 11% of the tumors overexpressed the protein, and the response rate was only about 4% (351).

In addition to its use as a maintenance therapy (245), the OvaRex anti-CA125 monoclonal antibody is being used alone and in combination with a variety of cytotoxic agents in the treatment of patients with recurrent disease (352,353) .

Intraperitoneal Therapy

For patients with minimal residual (<5 mm) or microscopic disease confined to the peritoneal cavity, consideration can be given to intraperitoneal chemotherapy or immunotherapy. The failure of second-line intravenous chemotherapy to control residual disease has led to the use of intraperitoneal therapies for small, persistent disease.

Intraperitoneal Chemotherapy

Cytotoxic chemotherapeutic agents, such as *cisplatin*, *5-fluorouracil*, *cytosine arabinoside* (*Ara-C*), *etoposide* (*VP-16*), and *mitoxantrone*, have been used for patients with persistent

epithelial ovarian cancer (354,355,356,357,358,359,360,361,362,363), and complete responses have been seen in patients who begin treatment with minimal residual disease. **The surgically documented response rates reported with this approach are about 20% to 40% for carefully selected patients, and the complete response rate is about 10% to 20%.** *Cisplatin* seems to be the best drug, although various combinations of agents (e. g., *cisplatin* plus *etoposide*) have been shown to have significant activity (356,357). Although it has been suggested that this approach produces a significant subsequent improvement in survival (359), there are no prospective phase III data, and the patients so treated tend to be those with a more favorable prognosis regardless of subsequent therapy.

Intraperitoneal Immunotherapy

Another approach is the use of intraperitoneal immunotherapy such as *interferon* (364,365,366,367,368,369,370). *Interferon* has been found to have some activity for patients with minimal residual disease (364,365). Intraperitoneal administration *interferon- α* , *interferon- γ* , *tumor necrosis factor*, and *interleukin-2* has been performed. **The response rate for the intraperitoneal cytokines, *interferon- α* and *interferon- γ* , is the same as that for the cytotoxic agents (i.e., 28% to 50%) (364,365,366,367,368,369,370).** The intraperitoneal administration of *interferon- α* has produced a 32% (9 of 28) surgically documented complete response rate, and a 50% (14 of 28) total response rate for patients with minimal residual disease after primary combination chemotherapy with *cisplatin* (364,369). This experience was replicated in a multi-institutional trial in which the surgically documented complete response rate was 28% in platinum-sensitive patients (365).

The interferons have been combined with cytotoxic agents in an effort to increase the overall response rates. In several trials, the combination of *cisplatin* and *interferon- α* seemed to produce a 50% complete response rate, which was greater than that produced by either single agent (367,368,369). Surgically documented responses to intraperitoneal therapy have been generally limited to patients with minimal residual disease (i.e., < 5 mm maximal tumor dimension) and patients whose tumors have been responsive to *cisplatin* chemotherapy.

Candidates for Intraperitoneal Therapy

Intraperitoneal treatment is not suitable for all patients because it can be cumbersome, requiring catheters that remain functional. Neither patients with extensive intraperitoneal adhesions nor patients with extraperitoneal disease are appropriate candidates. On the basis of these issues and the failure to achieve responses in most patients with bulky, *platinum*-refractory disease, second-line intraperitoneal chemotherapy and immunotherapy should still be considered experimental (371).

High-dose Chemotherapy and Autologous Bone

Marrow Transplantation

The use of high-dose chemotherapy and either autologous bone marrow transplantation (ABMT) or peripheral stem cell protection has been tested in patients with advanced ovarian cancer (372,373,374,375). A phase III randomized trial of 57 patients treated with high-dose chemotherapy (*cyclophosphamide* 6,000 mg/m² and *carboplatin* 1,600 mg/m²) with peripheral blood stem cell support as consolidation versus 53 patients treated with conventional dose maintenance (*cyclophosphamide* 600 mg/m² and *carboplatin* 300 mg/m²) has been reported (374). Only 43 of the 57 (75%) women completed the high-dose therapy, whereas 48 of 53 (92%) completed the standard dose regimen, and there was no statistically significant difference in progression-free and overall survival between the two groups of patients. A nonrandomized trial of ABMT for consolidation in 96 patients conducted at the MD Anderson Cancer Center showed a 6-year survival of 37%, but it is unclear if this would be survival advantage (375).

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Radiation Therapy

Whole-abdominal radiation therapy given as a salvage treatment has been shown to be associated with a relatively high morbidity. The principal problem associated with this approach is the development of acute and chronic intestinal morbidity. As many as 30% of patients treated with this approach develop intestinal obstruction, which necessitated exploratory surgery with potential morbidity (376).

Intestinal Obstruction

Patients with epithelial ovarian cancer often develop intestinal obstruction, either at the time of initial diagnosis or, more frequently, in association with recurrent disease

(142,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393). Obstruction may be related to a mechanical blockage or to carcinomatous ileus.

The intestinal blockage can be corrected in most patients whose obstruction appears at the time of initial diagnosis. However, the decision to perform an exploratory procedure to ease intestinal obstruction in patients with recurrent disease is more difficult. For patients whose life expectancy is very short (e.g., <2 months), surgical relief of the obstruction is not indicated (377). **In those whose projected life span is longer, features that predict a reasonable likelihood of correcting the obstruction include young age, good nutritional status, and the absence of rapidly accumulating ascites** (378).

For most patients with recurrent ovarian cancer who have intestinal obstruction, initial management should include proper radiographic documentation of the obstruction,

hydration, correction of any electrolyte disturbances, parenteral alimentation, and intestinal intubation. For some patients, the obstruction may be alleviated by this conservative approach. A preoperative upper gastrointestinal radiographic series and a barium enema will define possible sites of obstruction.

If exploratory surgery is deemed appropriate, the type of operation to be performed will depend on the site and the number of obstructions. **Multiple sites of obstruction are not uncommon in patients with recurrent epithelial ovarian cancer.** More than one half of the patients have small-bowel obstruction, one third have colonic obstruction, and one sixth have both (379,380,381,382,383). If the obstruction is principally contained in one area of the bowel (e.g., the terminal ileum), this area can either be resected or bypassed, depending on what is easier to accomplish safely. Intestinal bypass is generally less morbid than resection, and in patients with progressive cancer, the survival time after these two operations is the same (384,385,386,387,388,389,390).

If multiple obstructions are present, resection of several segments of intestine is usually not indicated, and intestinal bypass and/or colostomy should be performed. A gastrostomy may occasionally be useful in this circumstance (389), and this can usually be placed percutaneously (392).

Surgery for bowel obstruction in patients with ovarian cancer carries an operative mortality of about 10% and a major complications rate of about 30% (377,378,379,380,381,382,383,384,385,386,387,388,389,390). The need for multiple reanastomoses and prior radiation therapy increase the morbidity, which consists primarily of sepsis and enterocutaneous fistulae. The median survival ranges from 3 to 12 months, although about 20% of such patients survive longer than 12 months (391,392,393).

Survival

The prognosis for patients with epithelial ovarian cancer is related to several clinical variables. Survival analyses based on the most commonly used prognostic variables are presented (1,3,24,133,134,135,136,137). Including patients at all stages, patients younger than 50 years of age have a 5-year survival rate of about 40%, compared with about 15% for patients

older than 50 years. **The 5-year survival rate for carefully and properly staged patients with stage I disease is 76% to 93%, depending on the tumor grade. The 5-year survival for stage II is 60% to 74%. The 5-year survival rate for stage IIIa is 41%, for stage IIIb about 25%, for stage IIIc 23%, and for stage IV disease 11%** (Fig 35.13).

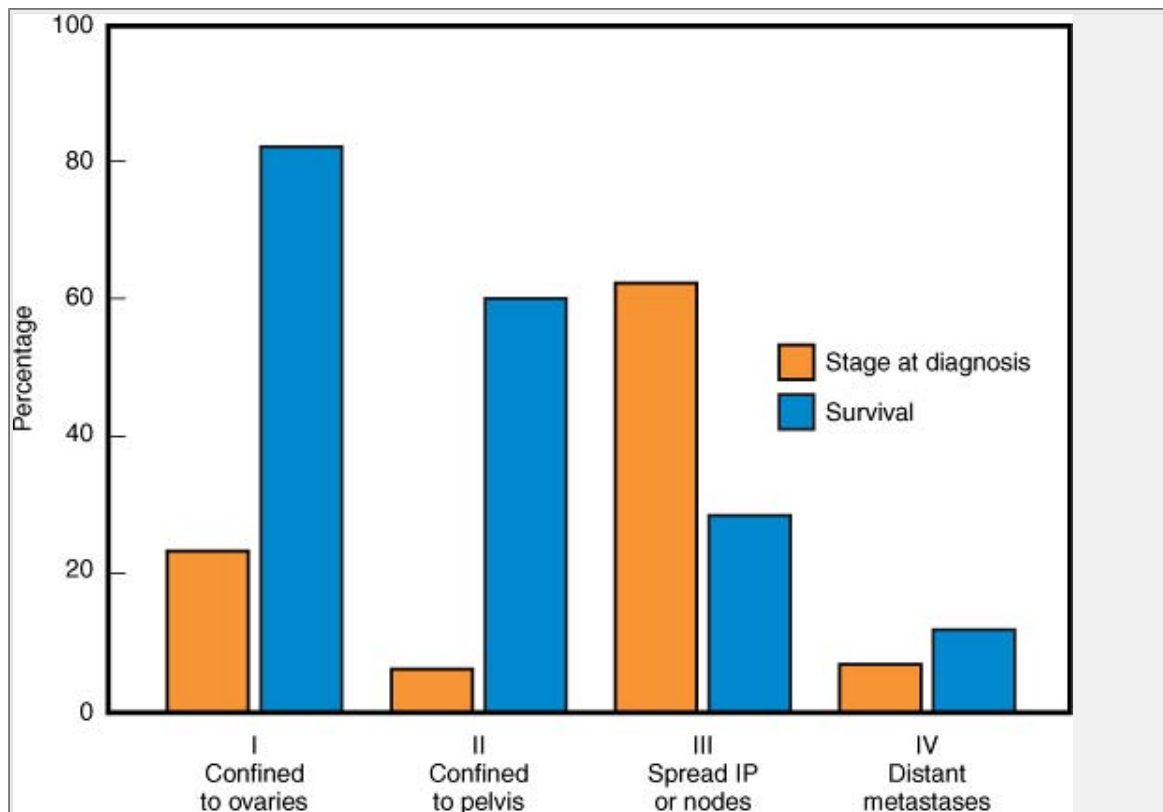


Figure 35.13 Survival of patients with epithelial ovarian cancer. The percentage of patients diagnosed at a particular stage is shown next to the 5-year survival by stage. *IP*, intraperitoneal. (From **Berek JS, Hacker NF**, eds. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:492, with permission.)

An analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database reveals a trend toward improved survival for ovarian cancer in the United States during the last period of analysis (1988 to 1994). In this cohort, the survival for stage I was 93%, for stage II 70%, for stage III 37%, and for stage IV 25% (394). Compared with the interval 1983 to 1987, there was a statistically significant improvement in survival for stages I, III, and IV disease.

Survival of patients with borderline tumors is excellent, with stage I lesions having a 98% 15-year survival (24). When all stages of borderline tumors are included, the 5-year survival rate is about 86% to 90%.

Regarding patients with invasive cancer, the 5-year survival rate for grade 1 epithelial ovarian cancers is about 91%, compared with about 74% for grade 2 and 75% for grade 3 (24,394). For stage II disease, the survivals are 69%, 60%, and 51%, respectively, for grades 1, 2, and 3. Examining stage III to IV patients, the 5-year survivals for grades 1, 2, and 3,

respectively, are 38%, 25%, and 19%. Patients with stage III disease with microscopic residual disease at the start of treatment have a 5-year survival rate of about 40% to 75%, compared with about 30% to 40% for those with optimal disease and only 5% for those with nonoptimal disease (136,137,162). Patients whose Karnofsky's index (KI) is low (<70) have a significantly shorter survival than those with a KI >70 (24).

Nonepithelial Ovarian Cancers

Compared with epithelial ovarian cancers, other malignant tumors of the ovary are uncommon. **Nonepithelial malignancies of the ovary account for about 10% of all ovarian cancers** (2,3,395). Nonepithelial ovarian cancers include malignancies of germ cell origin, sex cord–stromal cell origin, metastatic carcinomas to the ovary, and a variety of extremely rare ovarian cancers (e.g., sarcomas, lipoid cell tumors). Although there are many similarities in the presentation, evaluation, and management of these patients, these tumors also have many unique qualities that require a special approach (2,395,396,397,398).

Germ Cell Malignancies

Germ cell tumors are derived from the primordial germ cells of the ovary. Their incidence is only about one tenth the incidence of malignant germ cell tumors of the testis, so most of the advances in the management of these tumors have been extrapolations from experience with the corresponding testicular tumors. Although malignant germ cell tumors can arise in extragonadal sites such as the mediastinum and the retroperitoneum, most germ cell tumors arise in the gonad from undifferentiated germ cells. The variation in the site of these cancers is explained by the embryonic migration of the germ cells from the caudal part of the yolk sac to the dorsal mesentery before their incorporation into the sex cords of the developing gonads (2,3,395).

Classification

A histologic classification of ovarian germ cell tumors is presented in Table 32.5 (3,395). **Both α -fetoprotein (AFP) and human chorionic gonadotropin (hCG) are secreted by some germ cell malignancies; therefore, the presence of circulating hormones can be**

clinically useful in the diagnosis of a pelvic mass and in monitoring the course of a patient after surgery. Placental alkaline phosphatase (PLAP) and lactate dehydrogenase (LDH) are produced by up to 95% of dysgerminomas, and serial measurements of LDH may be useful for monitoring the disease. α_1 -Antitrypsin (AAT) can rarely be detected in association with germ cell tumors. When the histologic and immunohistologic identification of these substances in tumors is correlated, a classification

of germ cell tumors emerges (Fig. 35.14) (399).

Table 35.5 Histologic Typing of Ovarian Germ Cell Tumors	
1. Primitive germ cell tumors	3. Monodermal teratoma and somatic-type tumors associated with dermoid cysts
A. Dysgerminoma	A. Thyroid tumor
B. Yolk sac tumor	1. Struma ovarii
C. Embryonal carcinoma	a. Benign
D. Polyembryoma	b. Malignant
E. Non-gestational choriocarcinoma	B. Carcinoid
F. Mixed germ cell tumor	C. Neuroectodermal tumor
2. Biphasic or triphasic teratoma	D. Carcinoma
A. Immature teratoma	E. Melanocytic
B. Mature teratoma	F. Sarcoma
1. Solid	G. Sebaceous tumor
2. Cystic	H. Pituitary-type tumor
a. Dermoid cyst	I. Others (homunculus)
b. Fetiform teratoma	
Adapted from Tavassoli FA, Devilee P, eds. World Health Organization classification of tumours. <i>Pathology and Genetics of Tumors of the Breast and Female Organs</i> . Lyon: IARC Press, 2003.	

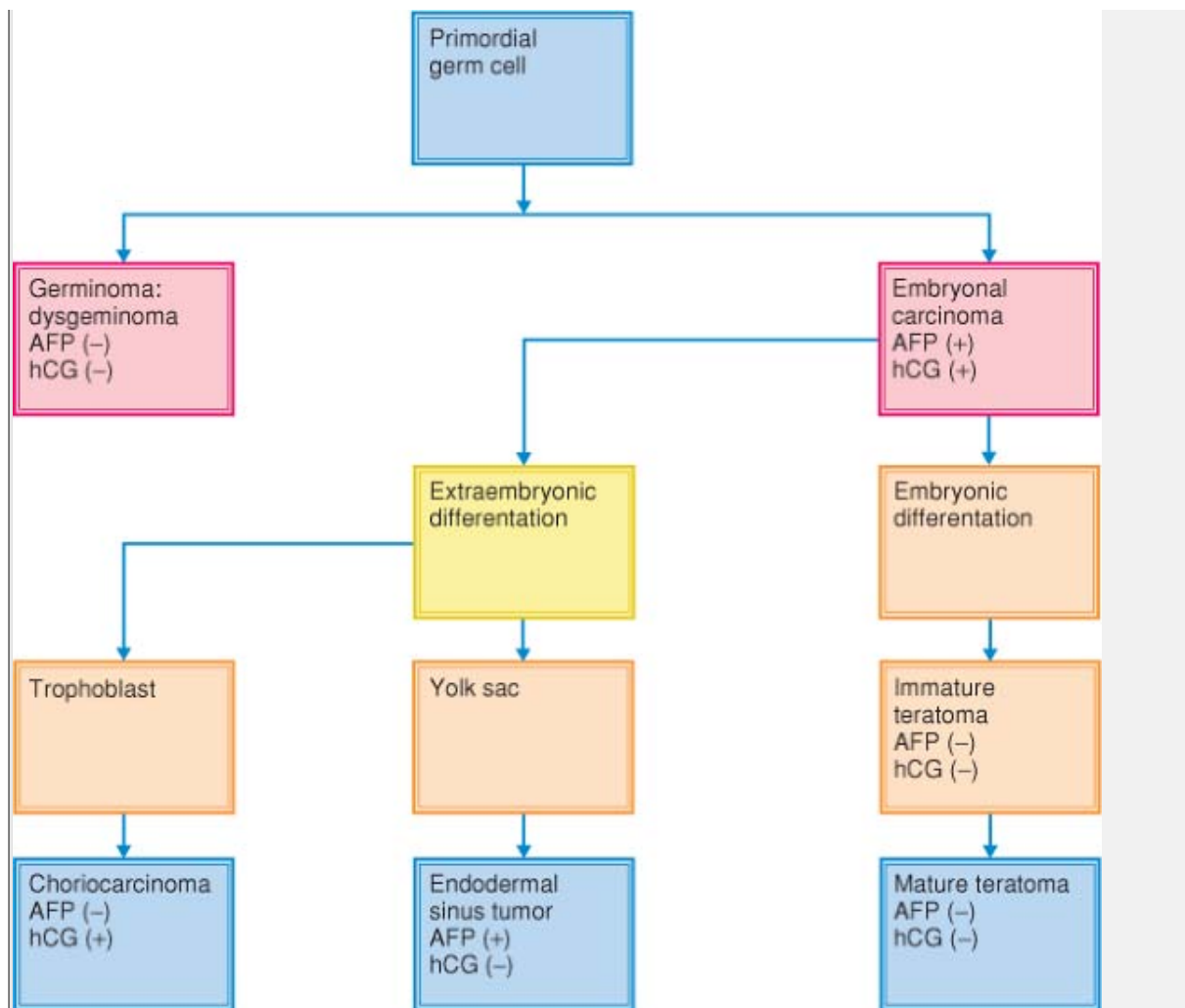


Figure 35.14 Relationship between types of pure malignant tumors. Germ cell tumors and their secreted marker substances. (From **Berek JS, Hacker NF.** *Practical gynecologic oncology*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2005:513, with permission.)

In this scheme, **embryonal carcinoma (a cancer composed of undifferentiated cells) synthesizes both hCG and AFP**, and this lesion is the progenitor of several other germ cell tumors (399). More differentiated germ cell tumors, such as the endodermal sinus tumor, which secretes AFP, and the choriocarcinoma, which secretes hCG, are derived from the extraembryonic tissues; the immature teratomas derived from the embryonic cells have lost the ability to secrete these substances. Pure germinomas do not secrete these markers.

Epidemiology

Although 20% to 25% of all benign and malignant ovarian neoplasms are of germ cell origin, only about 3% of these tumors are malignant (2,3). Germ cell malignancies account for fewer than 5% of all ovarian cancers in western countries. Germ cell malignancies represent up to 15% of ovarian cancers in Asian and African-American societies, where epithelial ovarian cancers are much less common.

In the first two decades of life, almost 70% of ovarian tumors are of germ cell origin, and one third of these are malignant (2,3,395). Germ cell tumors account for two thirds of the ovarian malignancies in this age group. Germ cell cancers also are seen in the third decade, but thereafter they become quite rare.

Clinical Features

Symptoms

In contrast to the relatively slow-growing epithelial ovarian tumors, germ cell malignancies grow rapidly and often are characterized by subacute pelvic pain related to capsular distention, hemorrhage, or necrosis. The rapidly enlarging pelvic mass may produce pressure symptoms on the bladder or rectum, and menstrual irregularities also may occur in menarcheal patients. Some young patients may misinterpret the early symptoms of a neoplasm as those of pregnancy, and this can lead to a delay in the diagnosis. Acute symptoms associated with torsion or rupture of the adnexa can develop. These symptoms may be confused with acute appendicitis. In more advanced cases, ascites may develop, and the patient can have abdominal distention (397).

Signs

For a patient with a palpable adnexal mass, the evaluation can proceed as outlined. Some patients with germ cell tumors will be premenarcheal and may require examination under anesthesia. **If the lesions are principally solid or a combination of solid and cystic, as might be noted on an ultrasonographic evaluation, a neoplasm is probable and a malignancy is possible** (see Fig. 14.8 and Chapter 14). During the remainder of the physical examination, effort should be directed to searching for signs of ascites, pleural effusion, and organomegaly.

Diagnosis

Adnexal masses measuring 2 cm or larger in premenarcheal girls or 8 cm or larger in other premenopausal patients will usually require surgical exploration. For young patients, blood tests should include serum hCG and AFP titers, a complete blood count, and

liver function tests. A radiograph of the chest is important because germ cell tumors can metastasize to the lungs or mediastinum. **A karyotype should be obtained preoperatively for all premenarcheal girls because of the propensity of these tumors to arise in dysgenetic gonads** (396,400). A preoperative CT scan or MRI may document the presence and extent of retroperitoneal lymphadenopathy or liver metastases; however, because these patients require surgical exploration, such extensive and time-consuming evaluation is unnecessary. If postmenarcheal patients have predominantly cystic lesions up to 8 cm in diameter, they may be observed or given oral contraceptives for two menstrual cycles (401).

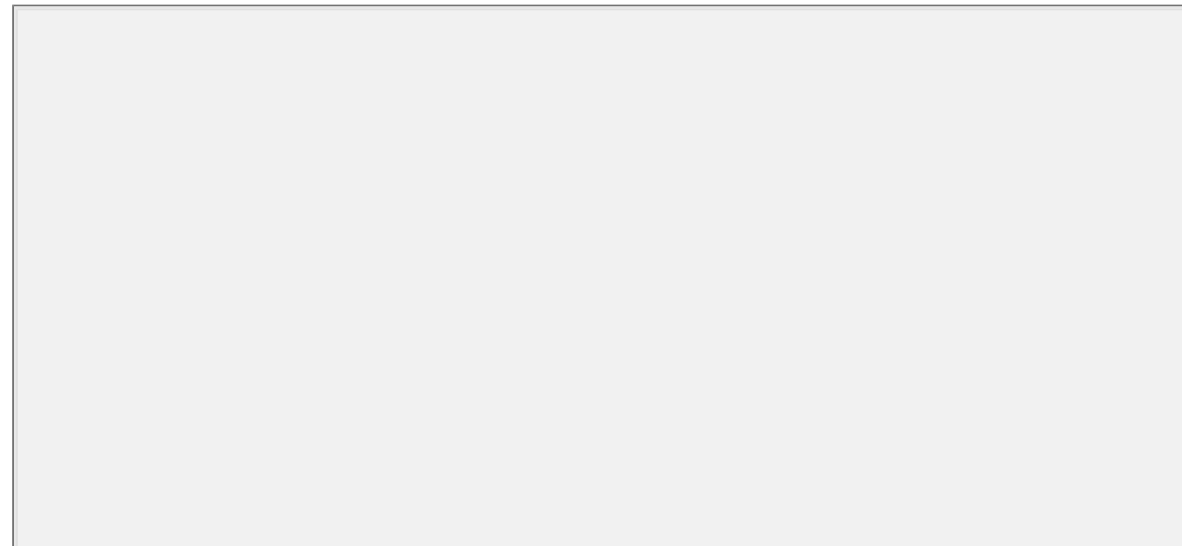
Dysgerminoma

Dysgerminoma is the most common malignant germ cell tumor, accounting for about 30% to 40% of all ovarian cancers of germ cell origin (2,3,399). The tumors represent only 1% to 3% of all ovarian cancers, but they represent as many as 5% to 10% of ovarian cancers in patients younger than 20 years. Seventy-five percent of dysgerminomas occur between the ages of 10 and 30 years, 5% occur before the age of 10 years, and they rarely occur after 50 years of age (2,3,397). Because these malignancies occur in young women, 20% to 30% of ovarian malignancies associated with pregnancy are dysgerminomas.

Dysgerminomas are found in both sexes and may arise in gonadal or extragonadal sites. The latter include the midline structures from the pineal gland to the mediastinum and the retroperitoneum. Histologically, they represent abnormal proliferations of the basic

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germ cell. In the ovary, the germ cells are encapsulated at birth (the primordial follicle), and the unencapsulated or free cells die. If either of the latter processes fails, it is conceivable that the germ cell could free itself of its normal control and multiply indiscriminately.



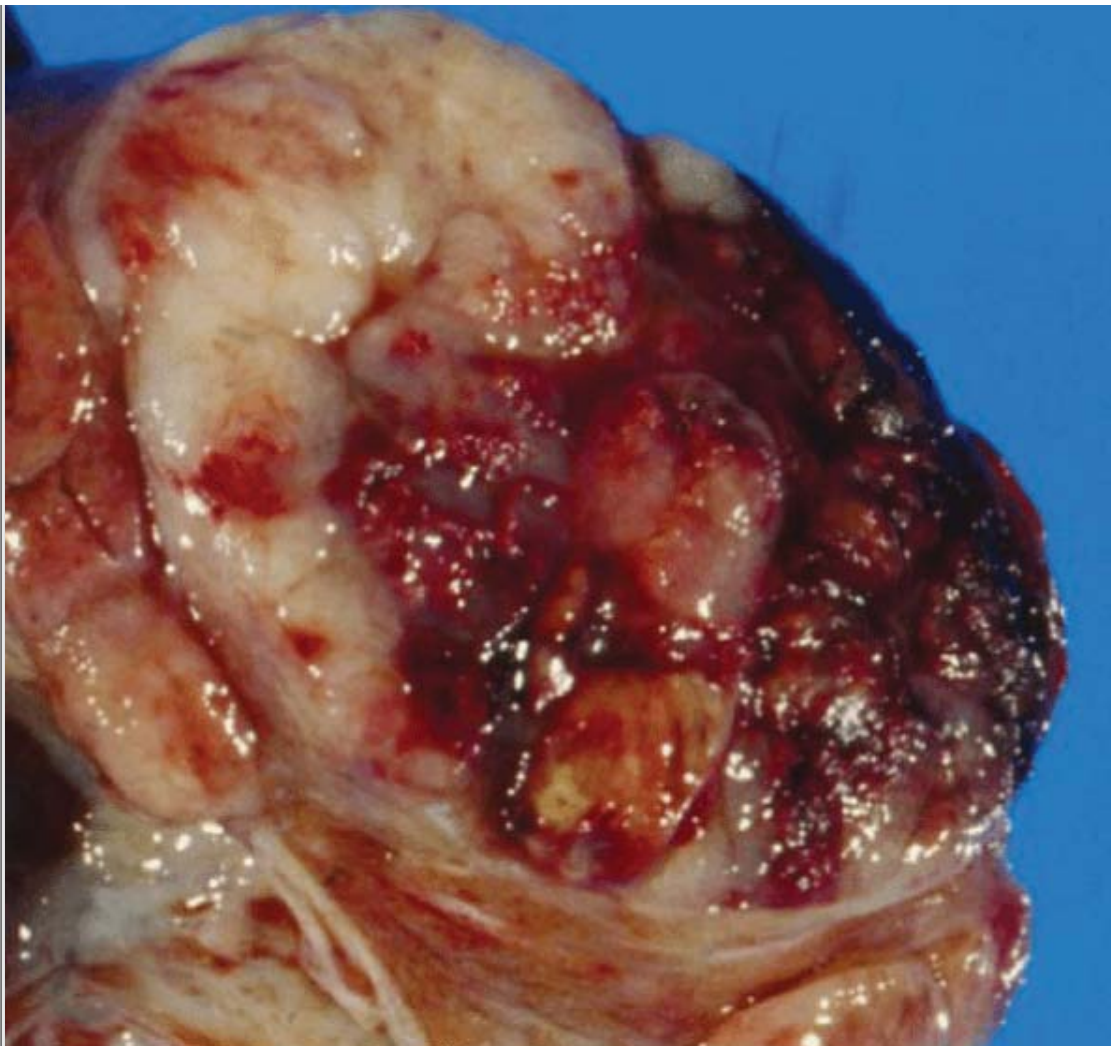


Figure 35.15 Dysgerminoma of the ovary. Note that the lesion is principally solid with some cystic areas and necrosis.

The size of dysgerminomas varies widely, but they are usually 5 to 15 cm in diameter (2,3). The capsule is slightly bosselated, and the consistency of the cut surface is spongy and gray-brown in color (Fig. 35.15).

The histologic characteristics of the dysgerminoma are very distinctive. The large round, ovoid, or polygonal cells have abundant, clear, very-pale-staining cytoplasm, large and irregular nuclei, and prominent nucleoli (Fig. 35.16). Mitotic figures are seen in varying numbers, although they are usually numerous. Another characteristic feature is the arrangement of the elements in lobules and nests separated by fibrous septa, which are often extensively infiltrated with lymphocytes, plasma cells, and granulomas with epithelioid

cells and multinucleated giant cells. When necrosis is extensive, the lesion may be confused with tuberculosis. Occasional dysgerminomas may contain syncytiotrophoblastic giant cells and may be associated with precocious puberty or virilization. The presence of these cells does not seem to alter the behavior of the tumor (2,3).

Because the dysgerminoma is a germ cell tumor and parthenogenesis (stimulation of the basic germ cell to atypical division) is the most commonly accepted genesis for the more immature teratomas, it is logical that these two tumors may coexist. Choriocarcinoma,

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endodermal sinus tumor, and other extraembryonal lesions are also commonly associated with the dysgerminoma.

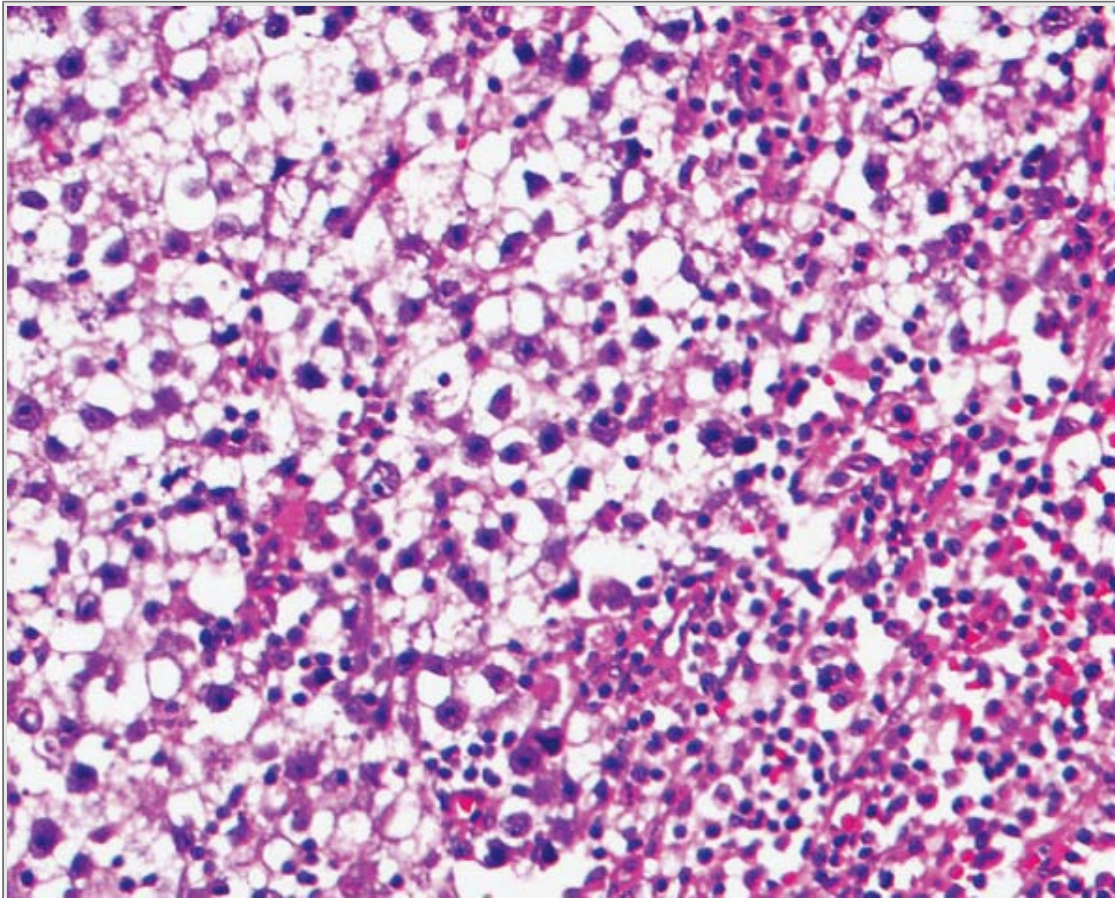


Figure 35.16 Dysgerminoma of ovary. Primitive germ cells are divided into clusters and lobules by fibrous septa rich in lymphocytes.

Approximately 5% of dysgerminomas are discovered in phenotypic women with

abnormal gonads (2,400,402). This malignancy can be associated with patients who have pure gonadal dysgenesis (46, XY, bilateral streak gonads), mixed gonadal dysgenesis (45, X/46, XY, unilateral streak gonad, contralateral testis), and the androgen insensitivity syndrome (46, XY, testicular feminization). Therefore, for premenarcheal patients with a pelvic mass, the karyotype should be determined (see Chapter 26).

For most patients with gonadal dysgenesis, dysgerminomas arise in gonadoblastomas, which are benign ovarian tumors that are composed of germ cells and sex cord stroma. If gonadoblastomas are left *in situ* in patients with gonadal dysgenesis, more than 50% will develop into ovarian malignancies (402).

About 65% of dysgerminomas are stage I (i.e., confined to one or both ovaries) at diagnosis (2,3,403,404,405,406,407,408). **About 85% to 90% of stage I tumors are confined to one ovary; 10% to 15% are bilateral. In fact, dysgerminoma is the only germ cell malignancy that has this significant rate of bilaterality. Other germ cell tumors are rarely bilateral.**

For patients whose contralateral ovary has been preserved, disease can develop in 5% to 10% of the retained gonads over the next 2 years (2). This figure includes those not given additional therapy, as well as patients with gonadal dysgenesis.

In the 25% of patients who are diagnosed initially with metastatic disease, the tumor most commonly spreads via the lymphatic system. It can also spread hematogenously or by direct extension through the capsule of the ovary with exfoliation and dissemination

P.1509

of cells throughout the peritoneal surfaces. Metastases to the contralateral ovary may be present when there is no other evidence of spread. An uncommon site of metastatic disease is bone; when metastasis to this site occurs, the lesions are seen principally in the lower vertebrae. Metastases to the lungs, liver, and brain are seen most often in patients with long-standing or recurrent disease. Metastasis to the mediastinum and supraclavicular lymph nodes is usually a late manifestation of disease (403,404).

Treatment

The treatment of patients with early dysgerminoma is primarily surgical, including resection of the primary lesion and proper surgical staging. Chemotherapy or radiation is administered to patients with metastatic disease. Because the disease principally affects girls and young women, special consideration must be given to the preservation of fertility and use of chemotherapy as needed whenever possible.

An algorithm for the management of ovarian dysgerminoma is presented in Fig. 35.17.

Surgery

The minimal surgical operation for ovarian dysgerminoma is a unilateral oophorectomy (405). If there is a desire to preserve fertility, the contralateral ovary, fallopian tube, and uterus should be left *in situ*, even in the presence of metastatic disease, because of the sensitivity of the tumor to chemotherapy. If fertility need not be preserved, it may be appropriate to perform a total abdominal hysterectomy and bilateral salpingo-oophorectomy for patients with advanced disease (407,408). For patients whose karyotype analysis reveals a Y chromosome, both ovaries should be removed, although the uterus may be left *in situ* for possible future embryo transfer (402). Whereas cytoreductive surgery is of unproved value, bulky disease that can be readily resected (e.g., an omental cake) should be removed during the initial operation.

In patients in whom the neoplasm appears on inspection to be confined to the ovary, a careful staging operation should be undertaken to determine the presence of any occult metastatic disease. All peritoneal surfaces should be inspected and palpated, and any suspicious lesions should be sampled for biopsy. Unilateral pelvic lymphadenectomy and at least careful palpation and biopsy of enlarged para-aortic nodes are particularly important parts of the staging. These tumors often metastasize to the para-aortic nodes around the renal vessels. Dysgerminoma is the only germ cell tumor that tends to be bilateral, and not all of the bilateral lesions are associated with obvious ovarian enlargement. Therefore, bisection of the contralateral ovary and excisional biopsy of any suspicious lesion are desirable (405,406,407,408). If a small contralateral tumor is found, it may be possible to resect it and preserve some normal ovary.

Many patients with a dysgerminoma will have a tumor that is apparently confined to one ovary and will be referred after unilateral salpingo-oophorectomy without surgical staging. The options for such patients are (i) repeat laparotomy for surgical staging, (ii) regular pelvic and abdominal CT scans, or (iii) adjuvant chemotherapy. As these are rapidly growing tumors, our preference is to perform regular surveillance. Tumor markers (LDH, AFP, and μ -hCG) should also be monitored in case occult mixed germ cell elements are present.

Radiation Therapy

Dysgerminomas are very sensitive to radiation therapy, and doses of 2,500 to 3,500 cGy may be curative, even for gross metastatic disease. Loss of fertility is a problem with radiation therapy, however, so radiation should rarely be used as first-line treatment (407).

Chemotherapy

There have been numerous reports of successful control of metastatic dysgerminomas with systemic chemotherapy, and this technique should now be regarded as the treatment of choice

the preservation of fertility (420,421,422,423).

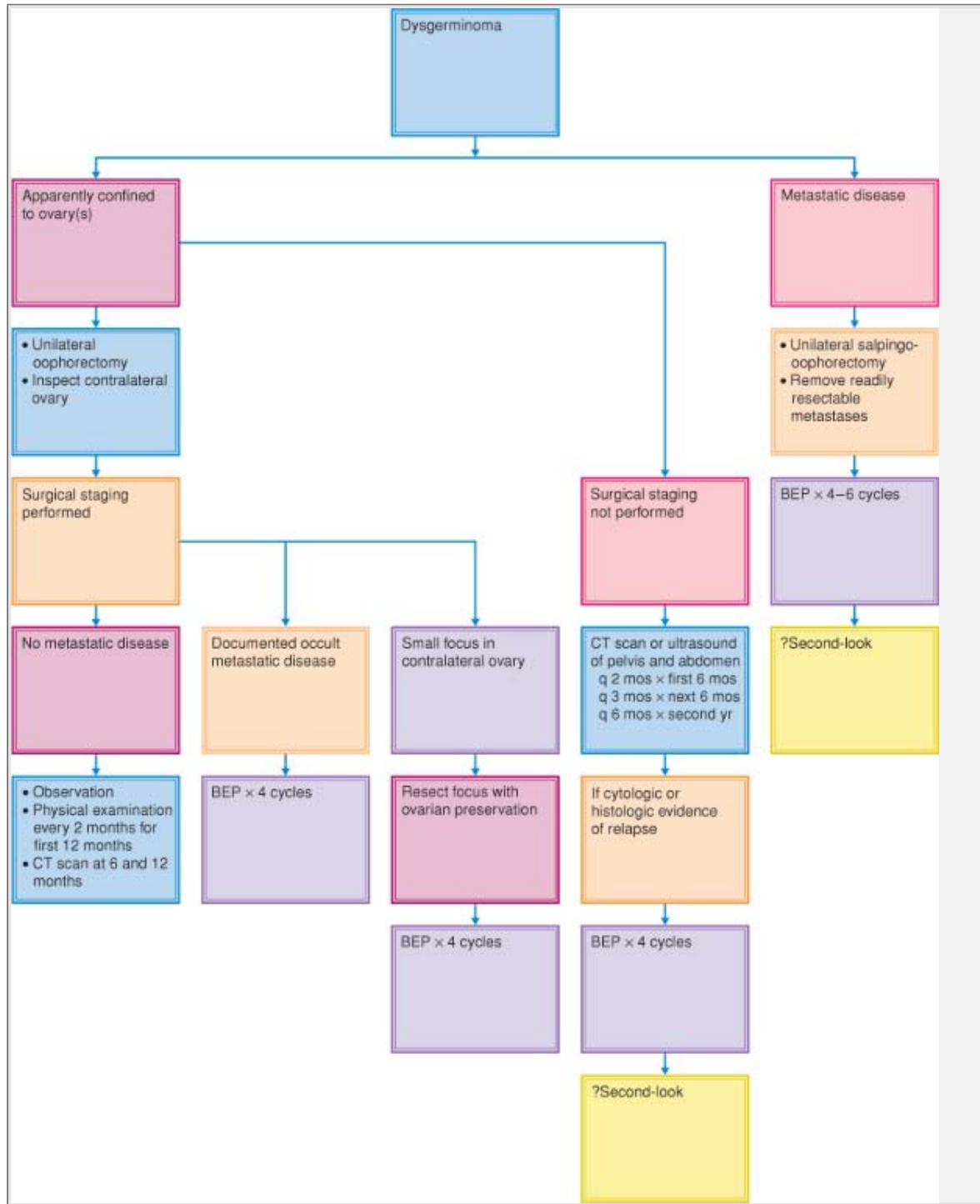


Figure 35.17 Management of dysgerminoma of the ovary. (From **Berek JS, Hacker NF.** *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:518, with permission.)

Table 35.6 Combination Chemotherapy for Germ Cell Tumors of the Ovary	
Regimen and Drugs	Dose and Schedule ^a
BEP	
Bleomycin	15 units/m ² /week × 5; then on day 1 of course 4
Etoposide	100 mg/m ² /day × 5 days every 3 weeks
Cisplatin	20 mg/m ² /day × 5 days, or 100 mg/m ² /day × 1 day every 3 weeks
VBP	
Vinblastine	0.15 mg/kg days 1 and 2 every 3 weeks
Bleomycin	15 units/m ² /week × 5; then on day 1 of course 4
Cisplatin	100 mg/m ² on day 1 every 3 weeks
VAC	
Vincristine	1–1.5 mg/m ² on day 1 every 4 weeks
Actinomycin D	0.5 mg/day × 5 days every 4 weeks
Cyclophosphamide	150 mg/m ² /day × 5 days every 4 weeks

^aAll doses given intravenously.

P.1510

P.1511

The most frequently used chemotherapeutic regimens for germ cell tumors are **BEP (bleomycin, etoposide, and cisplatin)**, **VBP (vinblastine, bleomycin, and cisplatin)**, and **VAC (vincristine, actinomycin, and cyclophosphamide)** (407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425) (Table 35.6).

The GOG studied three cycles of the EC regimen, consisting of *etoposide* (120 mg/m² intravenously on days 1, 2, and 3 every 4 weeks) and *carboplatin* (400 mg/m² intravenously on day 1 every 4 weeks) for patients with completely resected ovarian dysgerminoma, stages Ib, Ic, II, or III (416). The results showed a sustained disease-free remission rate of 100%.

For patients with advanced, incompletely resected germ cell tumors, the GOG studied *cisplatin*-based chemotherapy in two consecutive protocols (409,410). In the first study, patients received four cycles of *vinblastine* (12 mg/m² every 3 weeks), *bleomycin* (20 units/m² intravenously every week for 12 weeks), and *cisplatin* (20 mg/m² per day intravenously for 5 days every 3 weeks). Patients with persistent or progressive disease at second-look

laparotomy were treated with six cycles of VAC. In the second trial, patients received three cycles of BEP initially, followed by consolidation with VAC, which was later discontinued in patients with dysgerminomas (410). The VAC consolidation after BEP in patients with tumors other than dysgerminoma is still being investigated, but VAC does not appear to improve the outcome of the BEP regimen. A total of 20 evaluable patients with stage III and IV dysgerminoma were treated in these two protocols, and 19 are alive and free of disease after 6 to 68 months (median = 26 months). Fourteen of these patients had a second-look laparotomy, and all findings were negative. Another study at MD Anderson Cancer Center (413) used BEP in 14 patients with residual disease, and all patients were free of disease during long-term follow-up. **These results suggest that patients with advanced-stage, incompletely resected dysgerminoma have an excellent prognosis when treated with cisplatin-based combination chemotherapy. The best regimen is four cycles of BEP based on the data from testicular cancers** (424,425).

There appears to be no need to perform a second-look laparotomy in patients with dysgerminoma whose macroscopic disease was all resected during the primary operation (426,427,428). In patients with macroscopic residual disease at the start of chemotherapy, we

P.1512

prefer to perform a second-look operation, because second-line therapy is available and the earlier persistent disease is identified, the better the prognosis should be.

Recurrent Disease

About 75% of recurrences occur within the first year after initial treatment (2,395,396,397), the most common sites being the peritoneal cavity and the retroperitoneal lymph nodes. These patients should be treated with either radiation or chemotherapy, depending on their primary treatment. Patients with recurrent disease who have had no therapy other than surgery should be treated with chemotherapy. If prior chemotherapy with BEP has been given, POMB-ACE (*vincristine, bleomycin, cisplatin, etoposide, actinomycin D, and cyclophosphamide*) may be used (Table 35.7), and consideration should be given to the use of high-dose chemotherapy (e.g., with *carboplatin* and *etoposide*). Alternatively, radiation therapy is effective for this disease, with the major disadvantage being loss of fertility if pelvic and abdominal irradiation is required.

Pregnancy

Because dysgerminomas tend to occur in young patients, they may coexist with pregnancy. When a stage Ia cancer is found, the tumor can be removed intact and the pregnancy continued. For patients with more advanced disease, continuation of the pregnancy

P.1513

depends on the gestational age of the fetus. Chemotherapy can be given in the second and third trimesters in the same dosages as given for the nonpregnant patient without apparent detriment to the fetus (420).

Table 35.7 POMB-ACE Chemotherapy for Germ Cell Tumors of the Ovary

POMB

Day 1	<i>Vincristine</i> 1 mg/m ² IV; <i>methotrexate</i> 300 mg/m ² as a 12-hr infusion,
Day 2	<i>Bleomycin</i> 15 mg as a 24-hr infusion; <i>folinic acid</i> rescue started at 24 hrs after the start of <i>methotrexate</i> in a dose of 15 mg every 12 hrs for 4 doses
Day 3	<i>Bleomycin</i> infusion 15 mg by 24-hr infusion
Day 4	<i>Cisplatin</i> 120 mg/m ² as a 12-hr infusion, given with hydration and 3 g magnesium sulfate supplementation

ACE

Days 1–5	<i>Etoposide</i> (VP16-213) 100 mg/m ² , days 1–5
Days 3, 4, 5	<i>Actinomycin D</i> 0.5 mg IV, days 3, 4, and 5
Day 5	<i>Cyclophosphamide</i> 500 mg/m ² IV, day 5

OMB

Day 1	<i>Vincristine</i> 1 mg/m ² IV; <i>methotrexate</i> 300 mg/m ² as a 12-hr infusion
Day 2	<i>Bleomycin</i> 15 mg by 24-hr infusion; <i>folinic acid</i> rescue started at 24 hrs after start of <i>methotrexate</i> in a dose of 15 mg every 12 hrs for 4 doses
Day 3	<i>Bleomycin</i> 15 mg by 24-hr infusion

IV, intravenous.

The sequence of treatment schedules is two courses of POMB followed by ACE. POMB is then alternated with ACE until patients are in biochemical remission as measured by human chorionic gonadotropin (hCG) and α -fetoprotein (AFP), placental alkaline phosphatase (PLAP), and lactate dehydrogenase (LDH). The usual number of courses of POMB is three to five. Following biochemical remission, patients alternate ACE with OMB until remission has been maintained for approximately 12 weeks. The interval between courses of treatment is kept to the minimum (usually 9 to 11 days). If delays are caused by myelosuppression after courses of ACE, the first 2 days of etoposide are omitted from subsequent courses of ACE.

From **Newlands ES, Southall PJ, Paradinas FJ, et al.** Management of ovarian germ cell tumours. In: **Williams CJ, Kaikorian JG, Green MR, et al.**, eds. *Textbook of uncommon cancer*. New York, NY: John Wiley and Sons, 1988:47, with permission.

Prognosis

For patients whose initial disease is stage Ia (i.e., a unilateral

encapsulated dysgerminoma), unilateral oophorectomy alone results in a 5-year disease-free survival rate of greater than 95% (406,407). The features that have been associated with a higher tendency to recur include lesions larger than 10 to 15 cm in diameter, age younger than 20 years, and a microscopic pattern that includes numerous mitoses, anaplasia, and a medullary pattern (2,399).

Although in the past, surgery for advanced disease followed by pelvic and abdominal irradiation resulted in a 5-year survival rate of 63% to 83%, cure rates of 85% to 90% for this same group of patients are now being reported with the use of VBP, BEP, or EC combination chemotherapy (407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424).

Immature Teratomas

Immature teratomas contain elements that resemble tissues derived from the embryo. Immature teratomatous elements may occur in combination with other germ cell tumors as mixed germ cell tumors. The pure immature teratoma accounts for fewer than 1% of all ovarian cancers, but it is the second most common germ cell malignancy. This lesion represents 10% to 20% of all ovarian malignancies seen in women younger than 20 years and 30% of the deaths from ovarian cancer in this age group (2). About 50% of pure immature teratomas of the ovary occur in women between the ages of 10 and 20 years, and they rarely occur in postmenopausal women.

Pathology and Grading

Of fundamental importance in the understanding of the teratoma is a recognition of the maturation of the various elements. If maturation continues along normal lines, the mature or adult teratoma results, and the prognosis is excellent. Conversely, abnormal maturation of these elements produces undisciplined growth that can be fatal. Teratomas containing immature elements, although relatively rare, have been recognized more commonly during the past two decades (Fig. 35.18). Among the tumors with embryonal elements, those containing neural tissues demonstrate most clearly the importance of the ability to mature. Gliomatosis peritonei is the most dramatic demonstration of the significance of maturation, because most patients with these tumors have survived, even with this disseminated disease (3).

Immature teratomas are classified according to a grading system (grades 1 to 3) that is based on the degree of differentiation and the quantity of immature tissue (429). A determination of the amount of undifferentiated neural tissue is of prognostic importance. A grade 1 tumor is one in which less than one low-power microscopic field (LPF) contains immature neural elements, a grade 2 tumor has one to three LPFs with immature elements, and a grade 3 tumor has more than three LPFs with these elements. **The prognosis can be correlated with the grade determined by the quantity of these immature neural elements; with a**

higher grade, there is a poorer prognosis (2,3).

Previously, most malignant teratomas were classified as secondary neoplasms developing in a primarily benign teratoma. During the last decade, lesions composed primarily of immature embryonal or extraembryonal elements have become more prevalent, and the basic demonstration of malignancy is the inability of the tissue to mature rather than the presence of individual cell anaplasia (i.e., the mitotic activity may be low). This unique aspect is demonstrated by an absence of aneuploidy in the few cases that have been studied (3).

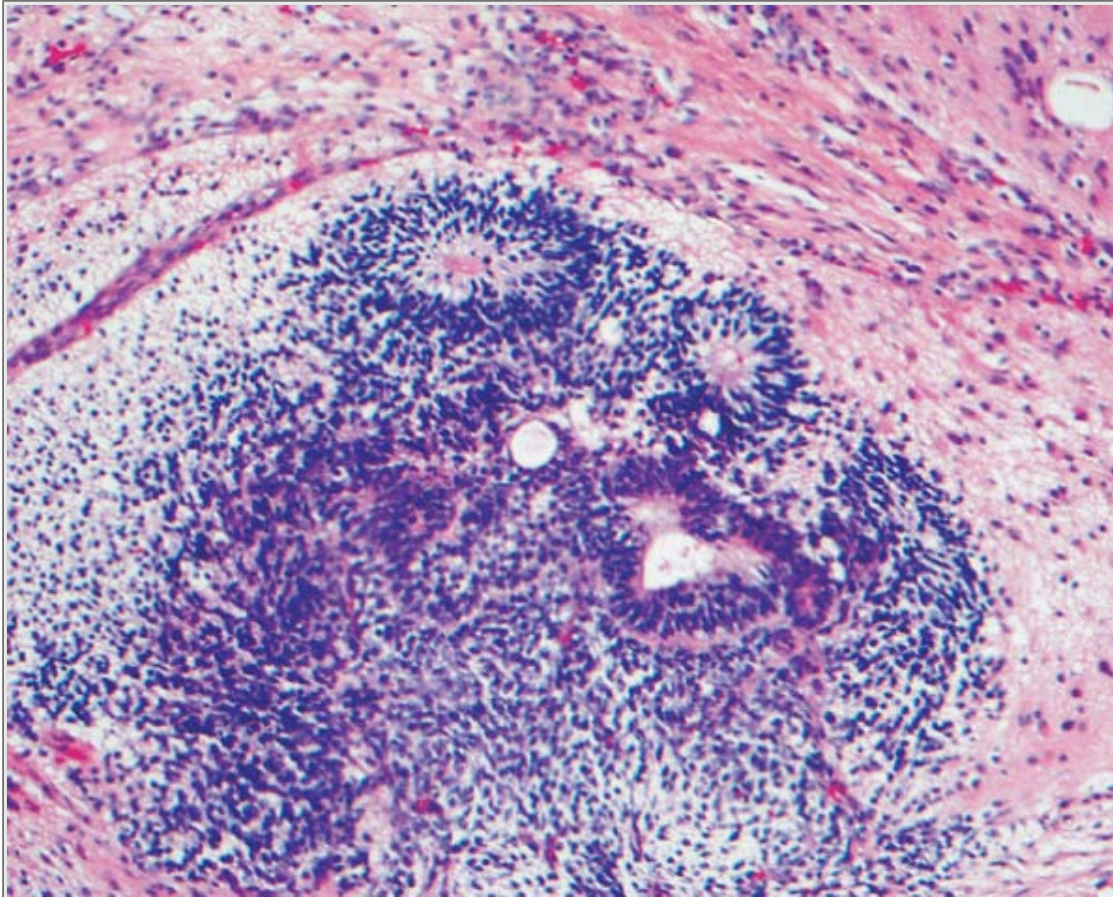


Figure 35.18 Ovarian teratoma. This tumor contains both mature and immature neural elements with a neural tube–like structure near its center.

Malignant change in benign cystic teratomas has been recorded as occurring in 0.5% to 2% of cases, usually in patients older than 40 years of age (429). The most common malignancy developing in the initially benign teratoma is squamous cell carcinoma.

Other neoplasms have been reported (e.g., melanomas, which may arise from the skin or retinal anlage, and sarcomas, including leiomyosarcomas and mixed mesodermal tumors) (2). Carcinomas may arise from any of the epithelial elements.

Diagnosis

The preoperative evaluation and differential diagnosis of immature teratomas are the same as for other germ cell tumors. Some of these lesions will contain calcifications similar to those of mature teratomas, which can be detected by a radiograph of the abdomen or by ultrasonography. Rarely, they are associated with the production of steroid hormones and can be accompanied by sexual pseudoprecocity (395,396,397). Tumor markers are negative unless a mixed germ cell tumor is present.

Treatment

Surgery

In a premenopausal patient whose lesion appears to be confined to a single ovary, unilateral oophorectomy and surgical staging should be performed. For a postmenopausal patient, a total abdominal hysterectomy and bilateral salpingo-oophorectomy may be performed. Contralateral involvement is rare, and routine resection or wedge biopsy of the contralateral ovary is unnecessary (3,429).

Any lesions on the peritoneal surfaces should be sampled and submitted for histologic evaluation. The most frequent site of dissemination is the peritoneum and, much less commonly, the retroperitoneal lymph nodes. Bloodborne metastases to organ parenchyma, such as the lungs, liver, or brain, are uncommon. When present, they are usually seen in patients with late or recurrent disease and most often in tumors that are poorly differentiated (i.e., grade 3).

P.1515

It is unclear whether debulking of metastatic implants enhances the response to combination chemotherapy (430,431,432,433,434,435,436,437). Unlike epithelial lesions, immature teratomas are much more chemosensitive. Because cure ultimately depends on the ability to deliver chemotherapy promptly, any surgical resection that may be potentially morbid and therefore delay chemotherapy should be resisted.

Chemotherapy

Patients with stage Ia, grade 1 tumors have an excellent prognosis, and no adjuvant therapy is required. For patients whose tumors are stage Ia, grades 2 or 3, adjuvant chemotherapy should be used

(411,412,413,413,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444).

Chemotherapy is also indicated for patients who have ascites, regardless of tumor grade. The most frequently used combination chemotherapeutic regimen in the past has been VAC (438,439,440). However, in a GOG study, the relapse-free survival rate in patients with incompletely resected disease was only 75% (440). The newer approach has been to incorporate *cisplatin* into the primary treatment of these tumors, and most of the experience has been with the VBP and BEP regimens (411,412,444). No direct comparison of these regimens with VAC has been reported, but the BEP combination can save some patients who have persistent or recurrent disease after VAC (434,435,444).

The GOG has been prospectively studying three courses of BEP therapy for patients with completely resected stage I, II, and III ovarian germ cell tumors (411,412,444). Overall, the toxicity has been acceptable, and 91 of 93 patients whose nondysgerminomatous tumors were treated are clinically free of disease. **Thus, the BEP regimen, which is used more extensively for testicular cancer, seems to be superior to the VAC regimen in the treatment of completely resected nondysgerminomatous germ cells tumors of the ovary.** Because some tumors can progress rapidly, treatment should be initiated as soon as possible after surgery, preferably within 7 to 10 days (445).

The switch from VBP to BEP has been prompted by the experience in patients with testicular cancer, in which the replacement of *vinblastine* with *etoposide* has been associated with a better therapeutic index (i.e., equivalent efficacy and lower morbidity), especially less neurologic and gastrointestinal toxicity. Furthermore, the use of *bleomycin* seems to be important for this group of patients. In a randomized study of three cycles of *etoposide* plus *cisplatin* with or without *bleomycin* (EP versus BEP) in 166 patients with germ cell tumors of the testes, the BEP regimen had a relapse-free survival rate of 84% compared with 69% for the EP regimen ($p = 0.03$) (424). In addition, *cisplatin* may be slightly better than *carboplatin* in the setting of metastatic germ cell tumors. One hundred ninety-two patients with germ cell tumors of the testes were entered into a study of four cycles of *etoposide* plus *cisplatin* (EP) versus four cycles of *etoposide* plus *carboplatin* (EC). There have been three relapses with the EP regimen versus seven with the EC regimen, although the overall survival of the two groups is identical thus far (425). In view of these results, **BEP is the preferred treatment regimen for patients with gross residual disease and has replaced the VAC regimen for patients with completely resected disease.**

The necessity of adjuvant chemotherapy for all patients with resected immature teratomas is uncertain. Several reports support the successful management of these patients with surgery alone (436,437,446). In the largest series, an intergroup study from the Pediatric Oncology Group and the Children's Cancer Group, 73 children with immature teratoma (44 of ovarian origin) underwent surgery followed by surveillance. With a median follow-up of 35 months, the overall 3-year event-free survival rates for all patients and those with ovarian teratomas were 93% and 100%, respectively. Thirteen of the 44 girls with an immature ovarian teratoma had microscopic foci of yolk sac tumor in the teratoma; one

developed recurrent disease and was successfully salvaged with *cisplatin*-based chemotherapy. Of note, 82% of the tumors were grade 1 or 2; however, 92% of those with foci of yolk sac tumor were grade 2 or 3.

Patients who have immature teratomas with malignant squamous elements seem to have a poorer prognosis than those whose tumors are without these elements (415,446,447). The treatment in these patients is also the BEP regimen.

Radiation Therapy

Radiation therapy is generally not used in the primary treatment of patients with immature teratomas. Furthermore, there is no evidence that the combination of chemotherapy and radiation has a higher rate of disease control than chemotherapy alone. Radiation therapy should be reserved for patients with localized persistent disease after chemotherapy (407,426).

Second-look Laparotomy

The need for a second-look operation has been questioned (427,428). It seems not to be justified in patients who have received chemotherapy in an adjuvant setting (i.e., stage Ia, grades 2 and 3), because chemotherapy in these patients is so effective. Second-look laparotomy in patients with macroscopic residual disease at the start of chemotherapy may be of value in selected patients, because there are no reliable tumor markers for this disease and such patients are at higher risk of failure.

If a second-look operation is performed, sampling of any peritoneal lesions should be performed and the retroperitoneal lymph nodes should be evaluated carefully. If only mature elements are found during the second-look procedure, chemotherapy should be discontinued. If the presence of persistent immature elements is documented, alternative chemotherapy should be employed. An enlarged contralateral ovary may contain a benign cyst or a mature cystic teratoma, which may be managed with an ovarian cystectomy (395,397).

Prognosis

The most important prognostic feature of the immature teratoma is the grade of the lesion (2,429). In addition, the stage of disease and the extent of tumor at the initiation of treatment have an impact on the curability of the lesion. Patients whose tumors have been incompletely resected before treatment have a significantly lower probability of 5-year survival than those whose lesions have been completely resected (i.e., 94% versus 50%) (397). Overall, the 5-year survival rate for patients with all stages of pure immature teratomas is 70% to 80%, and it is 90% to 95% for patients with surgically determined stage I

lesions (426,429,432).

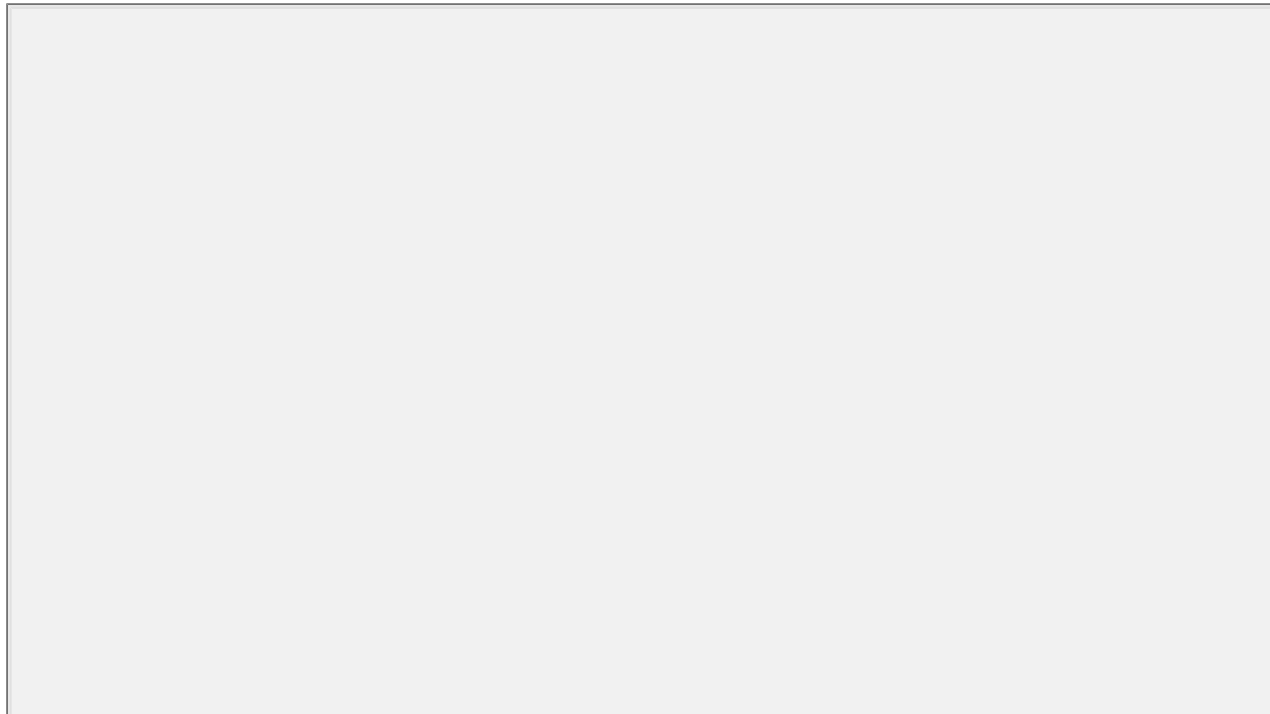
The degree or grade of immaturity generally correlates with the metastatic potential and curability. The 5-year survival rates for all stages combined have been reported to be 82%, 62%, and 30% for patients with grades 1, 2, and 3, respectively (429). Occasionally, these tumors are associated with mature or low-grade glial elements that have implanted throughout the peritoneum, and such patients usually have a favorable long-term survival (2,3).

Endodermal Sinus Tumors

Endodermal sinus tumors (EST) have also been referred to as *yolk sac carcinomas* because they are derived from the primitive yolk sac (2,3). These lesions are the third most frequent malignant germ cell tumors of the ovary. ESTs occur in patients with a median age of 16 to 18 years (2,3,448). About one third of the patients are premenarcheal at the time of diagnosis. Abdominal or pelvic pain is the most frequent initial symptom, occurring in about 75% of patients, whereas an asymptomatic pelvic mass is documented in 10% of patients (396).

Pathology

The gross appearance of an EST is soft grayish-brown. Cystic areas caused by degeneration are present in these rapidly growing lesions. The capsule is intact in most cases.



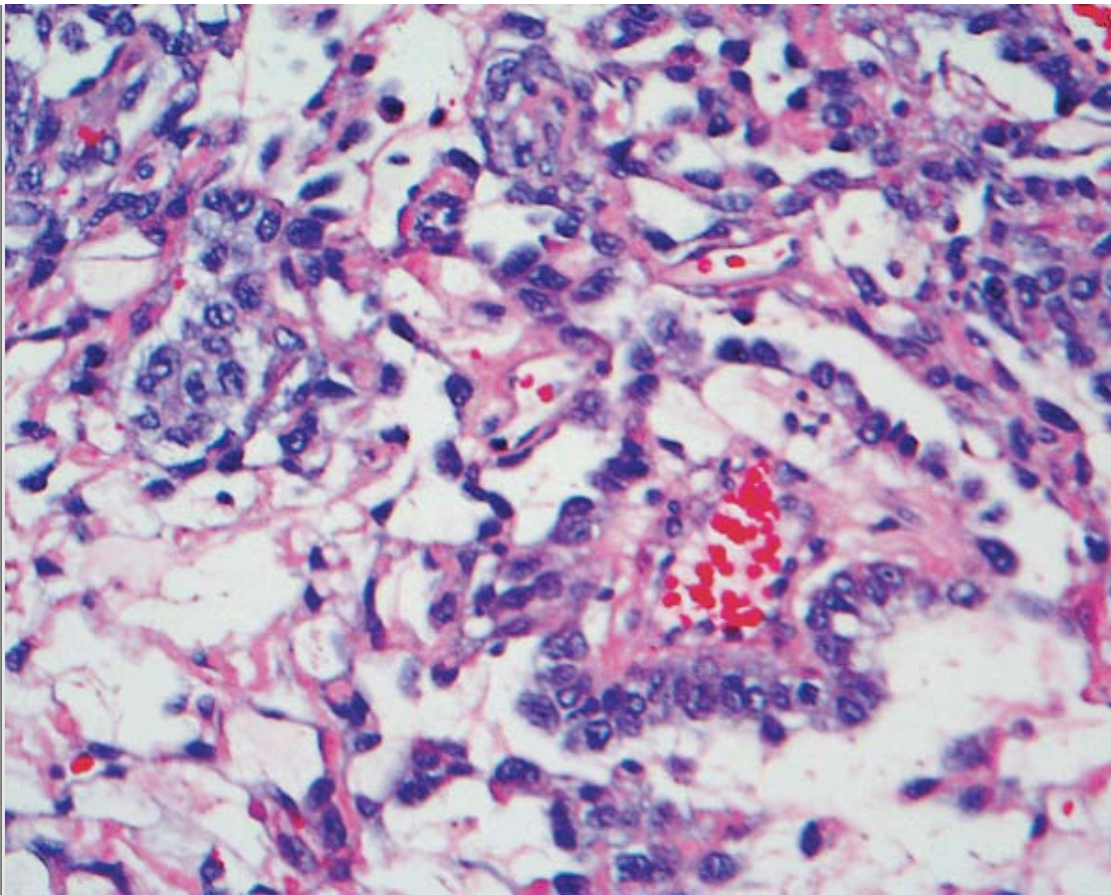


Figure 35.19 Endodermal sinus tumor of the ovary. Note the classic Schiller-Duval body with its central vessel and mantle of endoderm.

The EST is unilateral in 100% of cases; thus, biopsy of the opposite ovary in such young patients is contraindicated. The association of such lesions with gonadal dysgenesis must be appreciated, and chromosomal analysis should be performed preoperatively in premenarcheal patients (3).

Microscopically, the characteristic feature is the endodermal sinus, or *Schiller-Duval body* (Fig. 35.19). The cystic space is lined with a layer of flattened or irregular endothelium into which projects a glomeruluslike tuft with a central vascular core. These structures vary throughout the tumor, and the reticular, myxoid elements represent undifferentiated mesoblast. The lining of the papillary infolding and the cavity is irregular, with an occasional cell containing clear, glassy cytoplasm, simulating the hobnail appearance of the epithelium in clear cell tumors. The association of EST with dysgerminoma must be emphasized if diagnosis and therapy are to be optimal (2,3).

Most EST lesions secrete AFP and, rarely, they may elaborate detectable AAT. AFP can be demonstrated in the tumor by means of the immunoperoxidase technique. There is a good correlation between the extent of disease and the level of AFP, although discordance also has been observed. The serum level of these markers, particularly AFP, is useful in monitoring the patient's response to treatment (448,449,450,451,452).

Treatment

Surgery

The treatment of the EST consists of surgical exploration, unilateral salpingo-oophorectomy, and a frozen section for diagnosis. The addition of a hysterectomy and contralateral salpingo-oophorectomy does not alter outcome (397,450). Any gross metastases should be removed, if possible, but thorough surgical staging is not indicated because all patients need chemotherapy. At surgery, the tumors tend to be solid and large, ranging in size from 7 to 28 cm (median, 15 cm) in the GOG series (397,444).

P.1518

Bilaterality is not seen in these lesions, and the other ovary is involved with metastatic disease only when there are other metastases in the peritoneal cavity. Most patients have early-stage disease: 71%, stage I; 6%, stage II; and 23%, stage III (452).

Chemotherapy

All patients with ESTs are treated with either adjuvant or therapeutic chemotherapy. Before the routine use of combination chemotherapy for this disease, the 2-year survival rate was only about 25%. After the introduction of the VAC regimen, this rate improved to 60% to 70%, indicating the chemosensitivity of most of these tumors (439,440). Furthermore, with conservative surgery and adjuvant chemotherapy, fertility can be preserved as with other germ cell tumors.

VPB is a more effective regimen than VAC in the treatment of EST, particularly in the treatment of measurable or incompletely resected tumors (444). In the GOG series, only about 20% of patients with residual metastatic disease responded completely to the VAC regimen, whereas about 60% of those treated with VBP had a complete response (412). In addition, this regimen may save some patients in whom VAC therapy has failed.

Workers at the Charing Cross Hospital in London have developed the POMB-ACE regimen for high-risk germ cell tumors of any histologic type (453) (see Table 35.7). This protocol introduces seven drugs into the initial management, which is intended to minimize the chances of developing drug resistance. Drug resistance is particularly relevant for patients

with massive metastatic disease, and the POMB-ACE regimen may be used as primary therapy for such patients as well as for those with liver or brain metastases. The POMB schedule is only moderately myelosuppressive, so the intervals between each course can be kept to a maximum of 14 days (usually 9 to 11 days), thereby minimizing the time for tumor regrowth between courses. When *bleomycin* is given by a 48-hour infusion, pulmonary toxicity is reduced. With a maximum of 9 years of follow-up, the Charing Cross group has seen no long-term side effects for patients treated with POMB-ACE. Children have developed normally, menstruation has been physiologic, and several have completed normal pregnancies.

***Cisplatin*-containing combination chemotherapy, preferably BEP or POMB-ACE, should be used as primary chemotherapy for ESTs.** The optimal number of treatment cycles has not been established. The GOG protocols have used three to four treatment cycles given every 4 weeks (444,453). Alternatively, three cycles can be given to patients with stage I and completely resected disease, and two further cycles can be given after negative tumor marker status is achieved by patients with macroscopic residual disease before chemotherapy.

Second-look Laparotomy

The value of a second-look operation has yet to be established in patients with an EST. It seems reasonable to omit the operation for patients with pure low-stage lesions and for patients whose AFP values return to normal and remain normal for the balance of their treatment (451,452). There have been reported cases in which the AFP has returned to normal despite persistent measurable disease; some of these cases have been mixed germ cell tumors (452). For patients whose **AFP** levels do not return to normal, persistent disease can be assumed and alternative chemotherapy (e.g., **POMB-ACE**) can be offered.

Rare Germ Cell Tumors of the Ovary

Embryonal Carcinoma

Embryonal carcinoma of the ovary is an extremely rare tumor that is distinguished from a choriocarcinoma of the ovary by the absence of syncytiotrophoblastic and

cytotrophoblastic cells. The patients are very young; ages ranged between 4 and 28 years (median, 14 years) in two series (454). Older patients have been reported (455). Embryonal carcinomas may secrete estrogens, with the patient exhibiting symptoms and signs of precocious pseudopuberty or irregular bleeding (2). The clinical picture is otherwise similar to that of the EST. The primary lesions tend to be large, and about two thirds are confined to one ovary at the time of diagnosis. These lesions frequently secrete AFP and hCG, which are useful for following the response to subsequent therapy (451). **The treatment of embryonal carcinomas is the same as for the EST (i.e., a unilateral oophorectomy followed by combination chemotherapy with BEP)** (412,444). Radiation does not seem to

be useful for primary treatment.

Choriocarcinoma of the Ovary

Pure nongestational choriocarcinoma of the ovary is an extremely rare tumor. Histologically, it has the same appearance as gestational choriocarcinoma metastatic to the ovaries (456). Most patients with this cancer are younger than 20 years. The presence of hCG can be useful in monitoring the patient's response to treatment. **In the presence of high hCG levels, isosexual precocity has been seen to occur in about 50% of patients whose lesions appear before menarche** (456,457).

There are only a few limited reports on the use of chemotherapy for nongestational choriocarcinomas, but complete responses have been reported with the MAC (*methotrexate, actinomycin D, and cyclophosphamide*) regimen used in a manner described for gestational trophoblastic disease (458) (see Chapter 37). Alternatively, the BEP regimen can be used. The prognosis of ovarian choriocarcinomas has been poor, with most patients having metastases to organ parenchyma at the time of diagnosis.

Polyembryoma

Polyembryoma of the ovary is another extremely rare tumor, which is composed of "embryoid bodies." This tumor replicates the structures of early embryonic differentiation (i.e., the three somatic layers: endoderm, mesoderm, and ectoderm) (2,399). The lesion tends to occur in very young, premenarcheal girls with signs of pseudopuberty and elevated AFP and hCG titers. Anecdotally, the VAC chemotherapeutic regimen has been reported to be effective (399).

Mixed Germ Cell Tumors

Mixed germ cell malignancies of the ovary contain two or more elements of the lesions described above. In one series (458), the most common component of a mixed malignancy was dysgerminoma, which occurred in 80%, followed by EST in 70%, immature teratoma in 53%, choriocarcinoma in 20%, and embryonal carcinoma in 16%. **The most frequent combination was a dysgerminoma and an EST. The mixed lesions may secrete either AFP, hCG, or both or neither of these markers, depending on the components.**

These lesions should be managed with combination chemotherapy, preferably BEP. The serum marker, if positive initially, may become negative during chemotherapy, but this finding may reflect regression of only a particular component of the mixed lesion. Therefore, for these patients, a second-look laparotomy may be indicated to determine the precise response to therapy if macroscopic disease was present at initiation of chemotherapy.

The most important prognostic features are the size of the primary tumor and the

relative size of its most malignant component (458). For stage Ia lesions smaller than 10 cm, survival is 100%. Tumors composed of less than one third EST, choriocarcinoma, or grade 3 immature teratoma also have an excellent prognosis, but it is less favorable when these components constitute most of the mixed lesions.

Late Effects of Treatment of Malignant Germ Cell Tumors of the Ovary

Although there are substantial data regarding late effects of *cisplatin*-based therapy in men with testicular cancer, sparse information is available for women with ovarian germ cell tumors. Among the adverse events from chemotherapy reported in men are renal and gonadal dysfunction, neurotoxicity, cardiovascular toxicity, and secondary malignancies.

Gonadal Function

An important cause of infertility in patients with ovarian germ cell tumors is unnecessary bilateral salpingo-oophorectomy and hysterectomy. **Although temporary ovarian dysfunction or failure is common with *platinum*-based chemotherapy, most women will resume normal ovarian function, and childbearing is usually preserved** (400,406,408,460,461,462,463,464). In one representative series of 47 patients treated with combination chemotherapy for germ cell malignancies, 91.5% resumed normal menstrual function, and there were 14 healthy live births and no birth defects (422). Factors such as older age at initiation of chemotherapy, greater cumulative drug dose, and longer duration of therapy all have an adverse effect on future gonadal function (461).

Secondary Malignancies

An important cause of late morbidity and mortality in patients receiving chemotherapy for germ cell tumors is the development of secondary tumors. ***Etoposide* in particular has been implicated in the development of treatment-related leukemias** (465,466).

The chance of developing treatment-related leukemia following *etoposide* is dose related. **The incidence of leukemia is approximately 0.4% to 0.5%** (representing a 30-fold increased likelihood) in patients receiving a cumulative *etoposide* dose of less than 2,000 mg/m²(465), compared with as much as 5% (representing a 336-fold increased likelihood) in those receiving more than 2,000 mg/m²(465). In a typical three- or four-cycle course of BEP, patients receive a cumulative *etoposide* dose of 1,500 or 2,000 mg/m², respectively.

Despite the risk of secondary leukemia, risk-benefit analyses have concluded that *etoposide*-containing chemotherapy regimens are beneficial in advanced germ cell tumors; one case of treatment-induced leukemia would be expected for every 20 additionally cured patients

who receive BEP as compared with PVB. The risk-benefit balance for low-risk disease, or for high-dose *etoposide* in the salvage setting, is less clear (466).

Sex Cord—stromal

Sex cord—stromal tumors of the ovary account for about 5% to 8% of all ovarian Tumors malignancies (2,3,395,396,467,468,469,470,471,472,473). This group of ovarian neoplasms is derived from the sex cords and the ovarian stroma or mesenchyme. The tumors usually are composed of various combinations of elements, including the “female” cells (i.e., granulosa and theca cells) and “male” cells (i.e., Sertoli and Leydig cells), as well as morphologically indifferent cells. A classification of this group of tumors is presented in Table 35.8.

Granulosa-stromal Cell Tumors

Granulosa-stromal cell tumors include granulosa cell tumors, thecomas, and fibromas. The granulosa cell tumor is a low-grade malignancy; rarely, thecomas and fibromas have morphologic features of malignancy and then may be referred to as fibrosarcomas.

Granulosa cell tumors, which secrete estrogen, are seen in women of all ages. They are found in prepubertal girls in 5% of cases; the remainder are found in women throughout their reproductive and postmenopausal years (470). Granulosa cell tumors are bilateral in only 2% of patients.

Table 35.8 Sex Cord—stromal Tumors

1. Granulosa-stromal cell tumors

A. Granulosa cell tumor

B. Tumors in thecoma-fibroma group

1. Thecoma

2. Fibroma

3. Unclassified

2. Androblastomas; Sertoli-Leydig cell tumors

A. Well-differentiated

1. Sertoli cell tumor

2. Sertoli-Leydig cell tumor

3. Leydig cell tumor; hilus cell tumor

B. Moderately differentiated

C. Poorly differentiated (sarcomatoid)

D. With heterologous elements

3. Gynandroblastoma

4. Unclassified

From **Young RE, Scully RE**. Ovarian sex cord–stromal tumors: recent progress. *Int J Gynecol Pathol* 1980;1:153, with permission.

Pathology

Granulosa cell tumors range from a few millimeters to 20 centimeters or more in diameter. **The tumors are rarely bilateral**, and they have a smooth, lobulated surface. The solid portions of the tumor are granular, frequently trabeculated, and are commonly yellow or gray-yellow in color. The granulosa-theca cell tumor is probably the most inaccurately diagnosed lesion of the female gonad. Of 477 ovarian tumors from the Emil Novak Ovarian Tumor Registry diagnosed initially as granulosa-theca cell tumors, almost 15% were reclassified after histologic review. Lesions misdiagnosed as granulosa cell tumors included metastatic carcinomas, teratoid tumors, and poorly differentiated mesothelial tumors (467).

The classic granulosa cell is round or ovoid with scant cytoplasm. The nucleus contains compact, finely granular cytoplasm suggesting hyperchromatism (3). "Coffee bean" grooved nuclei are common, as are mitoses, thus simulating the corresponding elements in the normal, mature follicle. Conversely, if the epithelial elements are bizarre with atypical mitoses, the lesion should not be categorized as a poorly differentiated granulosa cell tumor but instead as an undifferentiated mesothelial neoplasm. **In the most common variety, the granulosa cells show a tendency to arrange themselves in small clusters or rosettes around a central cavity, so there is a resemblance to primordial follicles (i.e., Call-Exner bodies)** (Fig. 35.20). The stroma is similar to the theca and may be luteinized. In children and adolescents, the granular cell tumors are often cystic, contain luteinized cells, and can be associated with precocious puberty.

Diagnosis

Granulosa cell tumors, which secrete estrogen, are seen in women of all ages. They are found in prepubertal girls in 5% of cases; the remainder is distributed throughout the reproductive and postmenopausal years (470,471,472,473). They are bilateral in only 2% of patients.

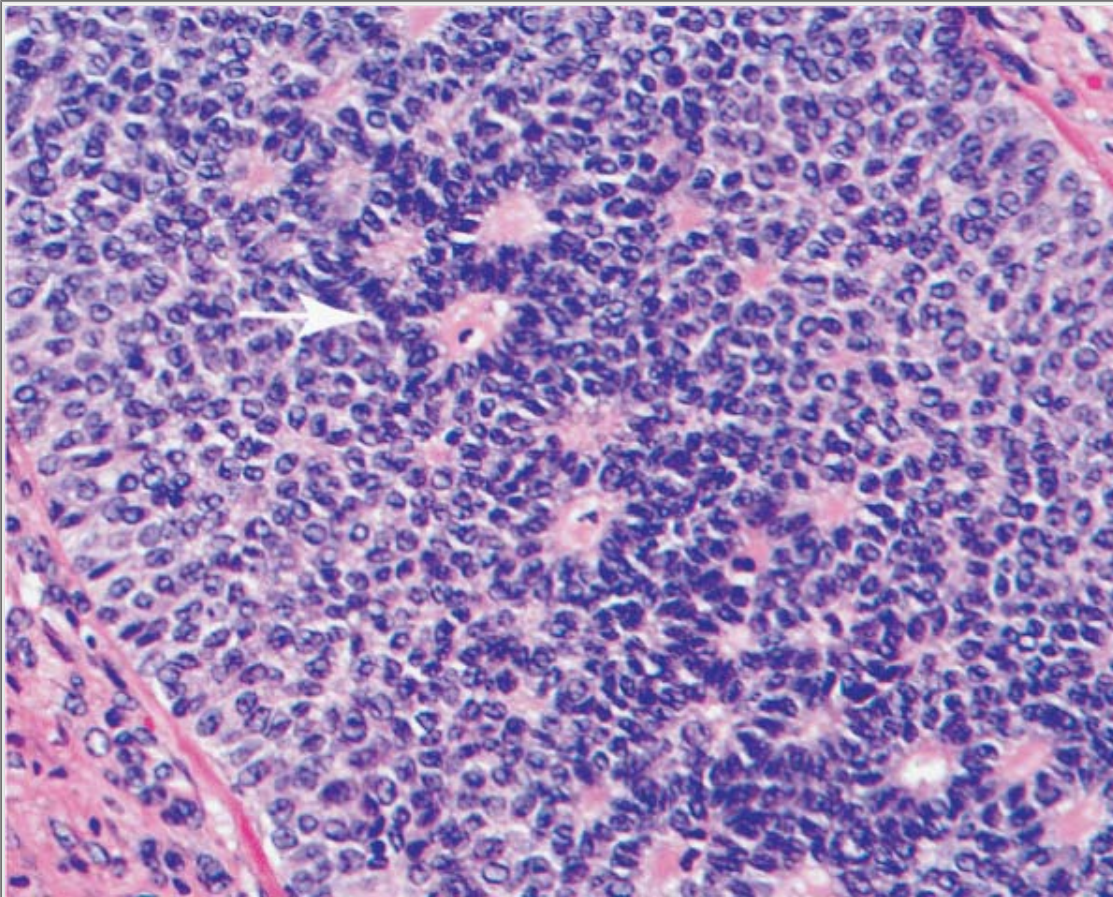


Figure 35.20 Granulosa cell tumor of the ovary. Note the classic Call-Exner bodies with a minimal stromal component in this tumor of folliculoid pattern. (Arrow points to an example.)

Of the rare prepubertal lesions, 75% are associated with sexual pseudoprecocity because of the estrogen secretion (470). For women of reproductive age, most patients have menstrual irregularities or secondary amenorrhea, and cystic hyperplasia of the endometrium is frequently present. For postmenopausal women, abnormal uterine bleeding is frequently the initial symptom. Indeed, the estrogen secretion in these patients can be sufficient to stimulate the development of endometrial cancer. **Endometrial cancer occurs in association with granulosa cell tumors in at least 5% of cases, and 25% to 50% are associated with endometrial hyperplasia** (2,456,467,468,469,470,470,472).

The other symptoms and signs of granulosa cell tumors are nonspecific and the same as most ovarian malignancies. Ascites is present in about 10% of cases, and rarely a pleural effusion is present (467,468,469,470). Granulosa tumors tend to be hemorrhagic; occasionally, they

rupture and produce a hemoperitoneum.

Granulosa cell tumors are usually stage I at diagnosis but may recur 5 to 30 years after initial diagnosis (469). The tumors may also spread hematogenously, and metastases can develop in the lungs, liver, and brain years after initial diagnosis. When granulosa cell tumors do recur, they can progress quite rapidly. Malignant thecomas are extremely rare, and their signs and symptoms, management, and outcome are similar to those of the granulosa cell tumors (467). **Inhibin is secreted by some granulosa cell tumors and is a useful marker for the disease** (474,475,476,477,478). An elevated serum inhibin level in a premenopausal woman presenting with amenorrhea and infertility is suggestive of a granulosa cell tumor (479).

Treatment

The treatment of granulosa cell tumors depends on the age of the patient and the extent of disease. For most patients, surgery alone is sufficient primary therapy; radiation and

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chemotherapy are reserved for the treatment of recurrent or metastatic disease (470,471,472,473,474,475,476,476,480,481,482,483).

Surgery

Because granulosa cell tumors are bilateral in only about 2% of patients, a unilateral salpingo-oophorectomy is appropriate therapy for stage Ia tumors in children or in women of reproductive age (468). At the time of laparotomy, if a granulosa cell tumor is identified by frozen section, a staging operation is performed, including an assessment of the contralateral ovary. If the opposite ovary appears enlarged, it should be sampled for biopsy. For perimenopausal and postmenopausal women for whom ovarian preservation is not important, a hysterectomy and bilateral salpingo-oophorectomy should be performed. **For premenopausal patients in whom the uterus is left *in situ*, an endometrial biopsy should be performed because of the possibility of a coexistent adenocarcinoma of the endometrium** (470).

Radiation Therapy

There is no evidence to support the use of adjuvant radiation therapy for granulosa cell tumors, although pelvic irradiation may help to palliate isolated pelvic recurrences (470,481).

Chemotherapy

There is no evidence that adjuvant chemotherapy will prevent recurrence of disease (483,484,485,486). Metastatic lesions and recurrences have been treated with a variety

of antineoplastic drugs. Although the data are inconclusive, four to six cycles of BEP in selected patients with stage III/IV disease is an acceptable regimen (480). In a GOG study, 37% (14 of 30) patients treated with BEP had a negative second-look laparotomy, and completely responding patients had a median time to progression of 24.4 months (487). The use of hormonal agents, such as progestins, antiestrogens, and aromatase inhibitors, have been suggested, but there are limited data available to suggest effectiveness (480).

Prognosis

Granulosa cell tumors have a prolonged natural history and a tendency toward late relapse, reflecting their low-grade biology. As such, 10-year survival rates of about 90% have been reported, with 20-year survival rates dropping to 75% (468,469,470,470,479,480). Most histologic types have the same prognosis, but patients with the more poorly differentiated diffuse or sarcomatoid type tend to do worse (467).

The DNA ploidy of the tumors has recently been correlated with survival. Holland and colleagues (484) reported DNA aneuploidy in 13 of 37 patients (35%) with primary granulosa cell tumors. The presence of residual disease was found to be the most important predictor of progression-free survival, but DNA ploidy was an independent prognostic factor. **Patients with residual-negative DNA diploid tumors had a 10-year progression-free survival of 96%.**

Juvenile granulosa cell tumors of the ovary are rare and make up less than 5% of ovarian tumors in childhood and adolescence (488). About 90% are diagnosed in stage I, and they have a favorable prognosis. The juvenile subtype behaves less aggressively than the adult type. Advanced-stage tumors have been successfully treated with platinum-based combination chemotherapy, e.g., BEP (480,487).

Sertoli-Leydig Tumors

Sertoli-Leydig tumors occur most frequently in the third and fourth decades of life; 75% of the lesions are seen in women younger than 40 years. These lesions are extremely rare and account for less than 0.2% of ovarian cancers (2). Sertoli-Leydig cell tumors are most frequently low-grade malignancies, although occasionally a poorly differentiated variety may behave more aggressively (489).

The tumors typically produce androgens, and clinical virilization is noted in 70% to 85% of patients (489). Signs of virilization include oligomenorrhea followed by amenorrhea, breast atrophy, acne, hirsutism, clitoromegaly, deepening of the voice, and a receding hairline. Measurement of plasma androgens may reveal elevated testosterone and androstenedione, with normal or slightly elevated dehydroepiandrosterone sulphate (2,492). Rarely, the Sertoli-Leydig tumor can be associated with manifestations of estrogenization (i.

e., isosexual precocity, irregular, or postmenopausal bleeding).

Treatment

Because these low-grade lesions are only rarely bilateral (<,1%), the usual treatment is unilateral salpingo-oophorectomy and evaluation of the contralateral ovary for patients who are in their reproductive years (3,470). For older patients, hysterectomy and bilateral salpingo-oophorectomy are appropriate (490,491).

There are insufficient data to document the utility of radiation or chemotherapy for patients with persistent disease, but some responses in patients with measurable disease have been reported with pelvic irradiation and the VAC chemotherapy regimen (3,397).

Prognosis

The 5-year survival rate is 70% to 90%, and recurrences thereafter are uncommon (3,492). Most fatalities occur in the presence of poorly differentiated lesions XS.

Uncommon Ovarian Cancers

There are several varieties of malignant ovarian tumors that together constitute only 0.1% of ovarian malignancies (2). Two of these lesions are the lipoid (or lipid) cell tumors and the primary ovarian sarcomas.

Lipoid Cell Tumors

Lipoid cell tumors are believed to arise in adrenal cortical rests that reside in the vicinity of the ovary. More than 100 cases have been reported, and bilateral disease has been noted in only a few (2). Most are associated with virilization and, occasionally, with obesity, hypertension, and glucose intolerance reflecting corticosteroid secretion. Rare cases of estrogen secretion and isosexual precocity have been reported.

Most of these tumors have benign or low-grade behavior, but about 20%, most of which are initially larger than 8 cm in diameter, are associated with metastatic lesions. Metastases are usually in the peritoneal cavity but rarely occur at distant sites. The primary treatment is surgical extirpation of the primary lesion. There are no data regarding the effectiveness of radiation or chemotherapy for this disease.

Sarcomas

Malignant mixed mesodermal sarcomas of the ovary are extremely rare; only about 100 cases have been reported. Most lesions are heterologous, and 80% occur in postmenopausal women. The signs and symptoms are similar to those of most ovarian

malignancies. These lesions are biologically aggressive, and most patients have evidence of metastases.

There is no effective treatment for ovarian sarcomas, and most patients die within 2 years. *Doxorubicin*, with or without *cyclophosphamide*, has produced an occasional partial response, and *cisplatin* is currently undergoing clinical trials (493,494,495,496,497). For patients in whom all macroscopic disease can be resected, we have observed disease-free survival of more than 3 years in two patients treated with six cycles of *cisplatin* and *epirubicin*.

Small Cell Carcinomas

This rare tumor occurs at an average age of 24 years (range 2 to 46 years) (498). The tumors are all bilateral. Approximately two thirds of the tumors are accompanied by paraendocrine hypercalcemia. This tumor accounts for one half of all of the cases of hypercalcemia associated with ovarian tumors. About 50% of the tumors have spread beyond the ovaries when they are diagnosed (498).

The management of these malignancies consists of surgery followed by platinum-based chemotherapy or radiation therapy or both. In addition to the primary treatment of the disease, control of the hypercalcemia may require aggressive hydration, loop diuretics, and the use of bisphosphonates or *calcitonin*. The prognosis tends to be poor, with most patients dying within 2 years of diagnosis in spite of treatment.

Metastatic Tumors

About 5% to 6% of ovarian tumors are metastatic from other organs, most frequently from the female genital tract, the breast, or the gastrointestinal tract (499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515). The metastases may occur from direct extension of another pelvic neoplasm, by hematogenous or lymphatic spread, or by transcoelomic dissemination, with surface implantation of tumors that spread in the peritoneal cavity.

Gynecologic

Nonovarian cancers of the genital tract can spread by direct extension or they may metastasize to the ovaries. Tubal carcinoma involves the ovaries secondarily in 13% of cases (2,3), usually by direct extension. Under some circumstances, it is difficult to know whether the tumor originated in the tube or in the ovary when both are involved. Cervical cancer spreads to the ovary only in rare cases (<1%), and most of these are of an advanced clinical stage or are adenocarcinomas. Although adenocarcinoma of the endometrium can spread and implant directly onto the surface of the ovaries in as many as 5%

of cases, two synchronous primary tumors probably occur with greater frequency (514). In these cases, an endometrioid carcinoma of the ovary is usually associated with the adenocarcinoma of the endometrium.

Nongynecologic

The frequency of metastatic breast carcinoma to the ovaries varies according to the method of determination, but the phenomenon is common (Fig. 35.21). In autopsy data of women who died of metastatic breast cancer, the ovaries were involved in 24% of cases, and 80% of the involvement was bilateral (499,500,501,502,503,504).

Similarly, when ovaries are removed to palliate advanced breast cancer, about 20% to 30% of the cases reveal ovarian involvement, 60% of those bilaterally. The involvement of ovaries in early-stage breast cancer seems to be considerably lower, but precise figures are not available. In almost all cases, either ovarian involvement is occult or a pelvic mass is discovered after other metastatic disease becomes apparent.

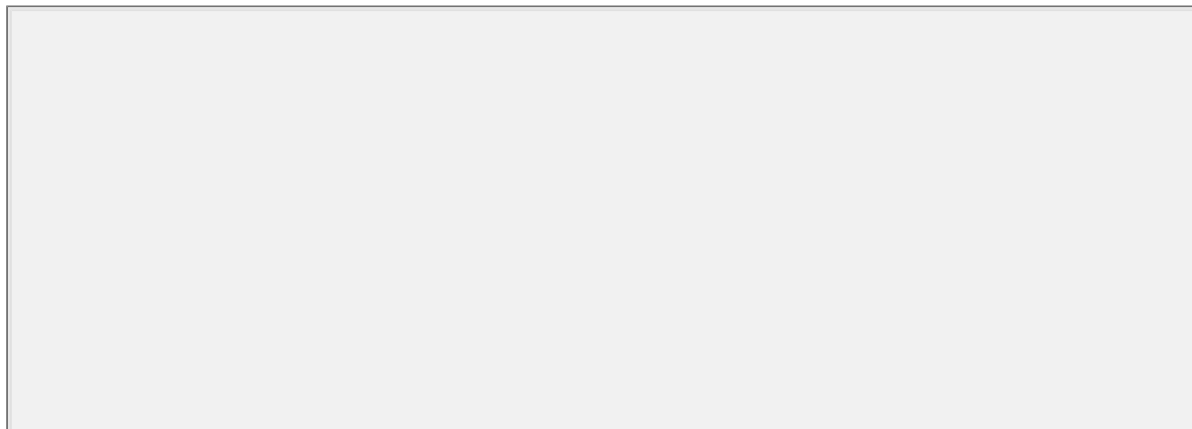
Krukenberg Tumor

The Krukenberg tumor, which can account for 30% to 40% of metastatic cancers to the ovaries, arises in the ovarian stroma and has characteristic mucin-filled, signet-ring cells (505,506,507) (Fig. 35.22). The primary tumor is most frequently located in the stomach and less commonly in the colon, breast, or biliary tract. Rarely, the cervix or the bladder may be the primary site. Krukenberg tumors can account for about 2% of ovarian cancers at some institutions, and they are usually bilateral. The lesions are usually not discovered until the primary disease is advanced and, therefore, most

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patients die of their disease within 1 year. In some cases, a primary tumor is never found.



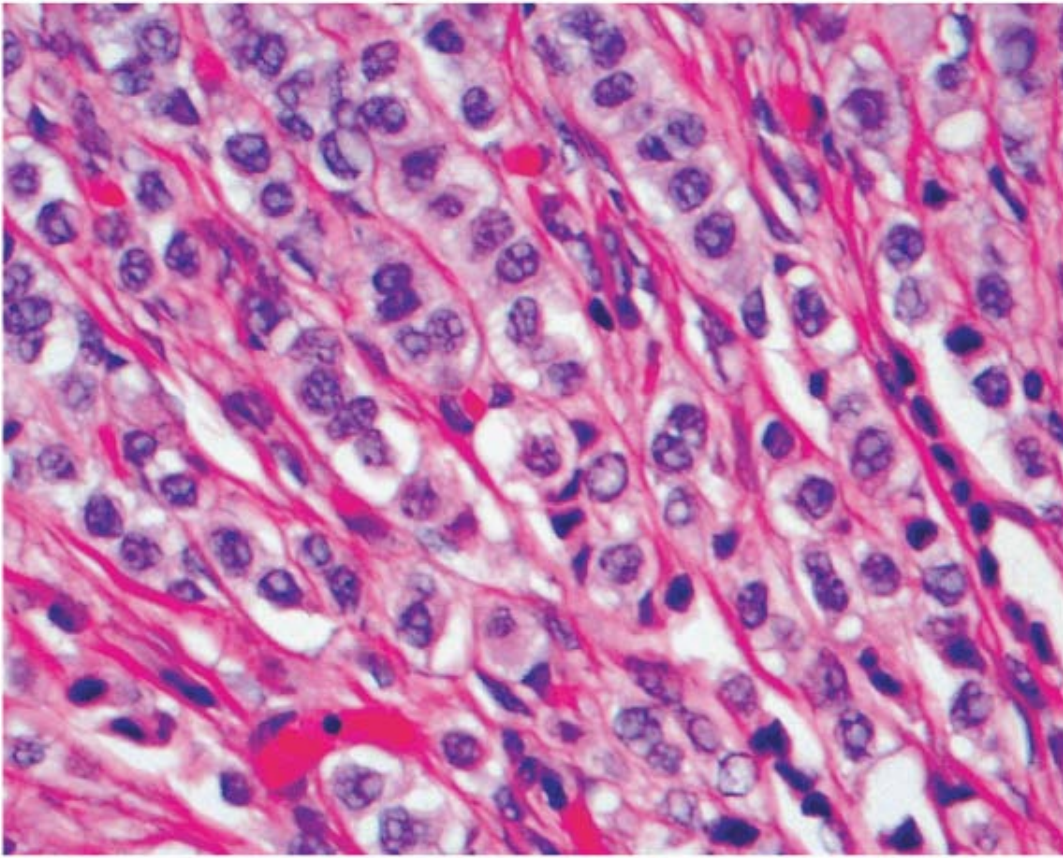


Figure 35.21 Metastatic carcinoma in the ovary. Note the "Indian file" pattern found in this metastatic breast carcinoma.

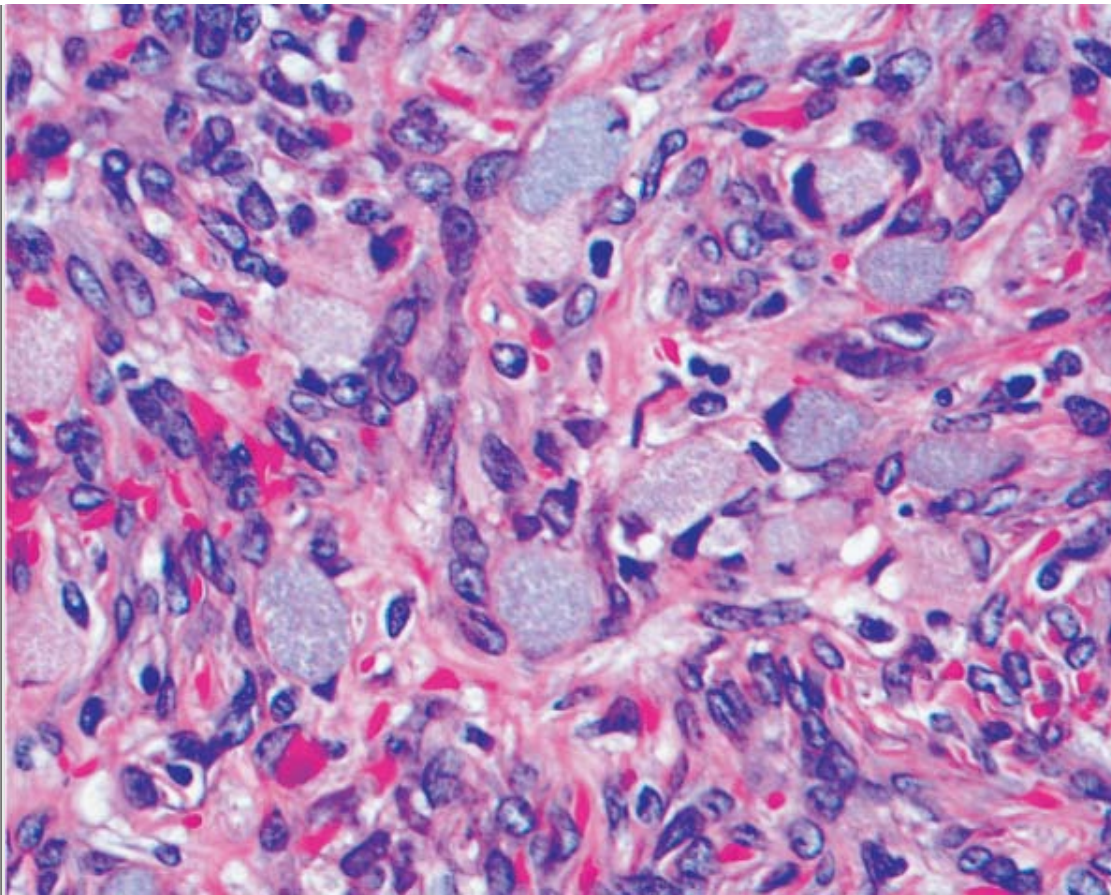


Figure 35.22 Krukenberg tumor of the ovary metastatic from a gastric carcinoma. Malignant cells have discrete vacuoles that push nuclei eccentrically, giving a signet-ring appearance. Mucicarmine stain demonstrates the cytoplasmic vacuoles to be mucin.

Other Gastrointestinal Tumors

In other cases of metastasis from the gastrointestinal tract to the ovary, the tumor does not have the classic histologic appearance of a Krukenberg tumor; most of these are from the colon and, less commonly, the small intestine. As many as 1% to 2% of women with intestinal carcinomas will develop metastases to the ovaries during the course of their disease (501). Before exploration for an adnexal tumor in a woman older than 40 years, a barium enema is indicated to exclude a primary gastrointestinal carcinoma with metastases to the ovaries, particularly if there are any gastrointestinal symptoms. Metastatic colon cancer can mimic a mucinous cystadenocarcinoma of the ovary histologically (500,501), and the histological distinction between the two can be difficult (508,509,510,511,512). Lesions that arise in the appendix may be associated with

ovarian metastasis and have frequently been confused with primary ovarian malignancies, especially when associated with pseudomyxoma peritonei (508,512). Therefore, it is reasonable to consider the performance of prophylactic bilateral salpingo-oophorectomy at the time of surgery for women with colon cancer (513).

Melanoma

Rare cases of malignant melanoma metastatic to the ovaries have been reported (515). In these circumstances, the melanomas are usually widely disseminated. Removal would be warranted for palliation of abdominal or pelvic pain, bleeding, or torsion. Malignant melanoma can arise rarely in a mature cystic teratoma (516).

Carcinoid Tumors

Metastatic carcinoid tumors represent fewer than 2% of metastatic lesions to the ovaries (517). Conversely, only about 2% of patients with primary carcinoids have evidence of ovarian metastasis, and only 40% of them have the carcinoid syndrome at the time of discovery of the metastatic carcinoid. However, in perimenopausal and postmenopausal women explored for an intestinal carcinoid, it is reasonable to remove the ovaries to prevent subsequent ovarian metastasis. Furthermore, the discovery of an ovarian carcinoid should prompt a careful search for a primary intestinal lesion (518).

Lymphoma and Leukemia

Lymphomas and leukemia can involve the ovary. When they do, the involvement is usually bilateral (519,520,521). About 5% of patients with Hodgkin disease will have lymphomatous involvement of the ovaries, but this involvement occurs typically with advanced-stage disease. **With Burkitt's lymphoma, ovarian involvement is very common. Other types of lymphoma involve the ovaries much less frequently, and leukemic infiltration of the ovaries is uncommon** (521). Sometimes the ovaries can be the only apparent site of involvement of the abdominal or pelvic viscera with a lymphoma; if this circumstance is found, a careful surgical exploration may be necessary. Intraoperatively, a hematologist-oncologist should be consulted to determine the need for these procedures if frozen section of a solid ovarian mass reveals a lymphoma. In general, most lymphomas no longer require extensive surgical staging, although biopsy of enlarged lymph nodes should generally be performed. In some cases of Hodgkin disease, a more extensive evaluation may be necessary. Treatment involves that of the lymphoma or leukemia in general. Removal of a large ovarian mass may improve patient comfort and facilitate a response to subsequent radiation or chemotherapy.

Fallopian Tube Cancer

Carcinoma of the fallopian tube accounts for 0.3% of all cancers of the female genital tract (2,3,522,523,524,525,526,527 528). In histologic features and behavior, fallopian tube carcinoma is

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similar to ovarian cancer; thus, the evaluation and treatment are also essentially the same (Fig. 35.23). The fallopian tubes are frequently involved secondarily from other primary sites, most often the ovaries, endometrium, gastrointestinal tract, or breast. They may also be involved in primary peritoneal carcinomatosis. Almost all cancers are of epithelial origin, most frequently of serous histology. Rarely, sarcomas have also been reported.

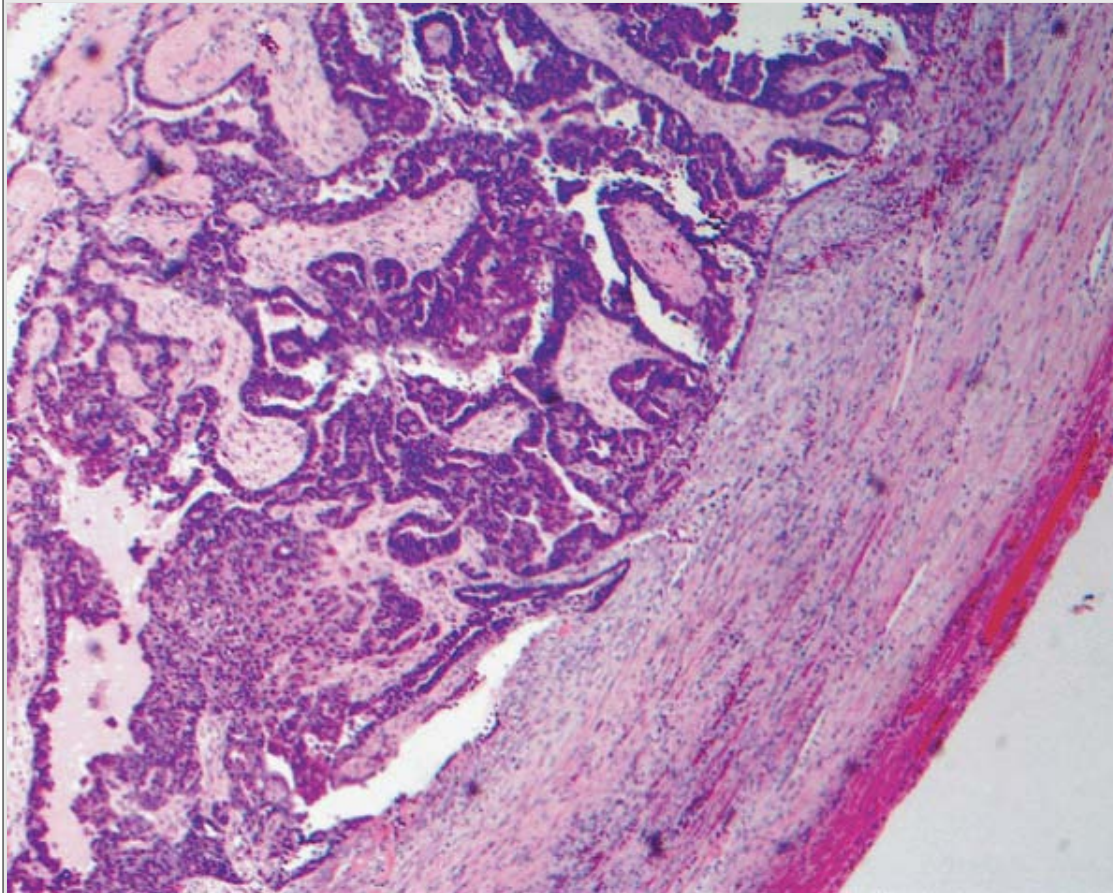


Figure 35.23 Carcinoma of the fallopian tube. This is the mixed papillary and the papillary-alveolar pattern.

Clinical Features

Tubal cancers are seen most frequently in the fifth and sixth decades, with a mean age

of 55 to 60 years (522). Women who have germline mutations in BRCA1 and BRCA2 are at substantially higher risk for developing fallopian tube carcinoma; therefore, prophylactic surgery in these women should include a complete removal of both tubes along with the ovaries (66,529).

Symptoms and Signs

The classic triad of symptoms and signs associated with fallopian tube cancer is (i) a prominent watery vaginal discharge (i.e., hydrops tubae profluens), (ii) pelvic pain, and (iii) a pelvic mass. However, this triad is noted in fewer than 15% of patients (3).

Vaginal discharge or bleeding is the most common symptom reported by patients with tubal carcinoma and is documented in more than 50% of patients (3,523).

Lower abdominal or pelvic pressure and pain also are noted in many patients. However, the symptoms may be rather vague and nonspecific. For perimenopausal and postmenopausal women with unusual, unexplained, or persistent vaginal discharge, even in the absence of bleeding, the clinician should be concerned about the possibility of occult tubal cancer.

Fallopian tube cancer is often found incidentally in asymptomatic women at the time of abdominal hysterectomy and bilateral salpingo-oophorectomy.

On examination, a pelvic mass is present in about 60% of patients, and ascites may be present if advanced disease exists. For patients with tubal carcinoma, the results of dilation and curettage will be negative (525), although abnormal or adenocarcinomatous cells may be seen in cytologic specimens obtained from the cervix in 10% of patients.

Spread Pattern

Tubal cancers spread in much the same manner as epithelial ovarian malignancies, principally by the transcoelomic exfoliation of cells that implant throughout the peritoneal cavity. In about 80% of the patients with advanced disease, metastases are confined to the peritoneal cavity at the time of diagnosis (524).

The fallopian tube is richly permeated with lymphatic channels, and spread to the para-aortic and pelvic lymph nodes is common. Metastases to the para-aortic lymph nodes have been documented in at least 33% of the patients with all stages of disease (528).

Staging

Fallopian tube cancer is staged according to FIGO (522,527). The staging is based on the surgical findings at laparotomy (Table 35.9). According to this system, about 20% to 25% of patients have stage I disease, 20% to 25% have stage II disease, 40% to 50% have stage

III disease, and 5% to 10% have stage IV disease (522). A somewhat lower incidence of advanced disease is seen in these patients than in patients with epithelial ovarian carcinomas, presumably because of the earlier occurrence of symptoms, particularly vaginal bleeding or unusual vaginal discharge. Findings on transvaginal ultrasonography and CT scan may be suspicious for tubal carcinomas (530).

Treatment

The treatment of this disease is the same as that of epithelial ovarian cancer (522,525,531,532,533,534,535,536,537). Exploratory laparotomy is necessary to remove the primary tumor, to stage the disease, and to resect metastases. After surgery, the most frequently employed treatment is *carboplatin* and *paclitaxel* chemotherapy

Surgery

Patients with tubal carcinoma should undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy (3). If there is no evidence of gross tumor spread, a staging operation is performed. The retroperitoneal lymph nodes should be adequately evaluated, and peritoneal cytologic studies and biopsies should be performed, along with an infracolic omentectomy.

In patients with metastatic disease, an effort should be made to remove as much tumor bulk as possible. The role of cytoreductive surgery in this disease is unclear, but extrapolation from the experience with epithelial ovarian cancer indicates that significant benefit might be expected, particularly if all macroscopic disease can be resected (532).

Chemotherapy

As with epithelial ovarian cancer, the most active agents are platinum and the taxanes. Experience with *cisplatin* and paclitaxel indicates that complete responses can be obtained (531,532). **Therefore, the recommended treatment for fallopian tube cancer is the same as that for epithelial ovarian cancer, i.e., platinum and taxane-based chemotherapy.** A variety of other chemotherapeutic agents that are effective against recurrent ovarian cancer appear to be active in recurrent or persistent fallopian tube carcinomas. These agents include *docetaxel*, *etoposide*, *topotecan*, *gemcitabine* and *liposomally encapsulated doxorubicin* (533,534,535,536,537). As data on well-staged lesions are scarce, it is unclear whether patients with disease confined to the fallopian tube (i.e., a stage Ia, grade 1 or 2 carcinoma) benefit from additional therapy.

Table 35.9 Modified FIGO Staging of Fallopian Tube Cancer (Based on Operative Findings before Debulking and Pathologic Findings)

Stage 0	Carcinoma <i>in situ</i>^a(limited to tubal mucosa).^b
Stage I	Growth is limited to the fallopian tubes.
Ia	Growth is limited to one tube with extension into the submucosa^c and/or muscularis but not penetrating the serosal surface; no ascites.
Ib	Growth is limited to both tubes with extension into the submucosa ^c and/or muscularis but not penetrating the serosal surface; no ascites.
Ic	Tumor either stage Ia or Ib but with tumor extension through or onto the tubal serosa; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both fallopian tubes with pelvic extension.
IIa	Extension and/or metastasis to the uterus and/or ovaries.
IIb	Extension to other pelvic tissues.
IIc	Tumor either stage IIa or IIb but with tumor extension through or onto the tubal serosa; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involves one or both fallopian tubes with peritoneal implants outside of the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumor appears limited to the true pelvis but with histologically proven malignant extension to the small bowel or omentum.
IIIa	Tumor is grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
IIIb	Tumor involving one or both tubes with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Lymph nodes are negative.
IIIc	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both fallopian tubes with distant metastases. If pleural effusion is present, there must be positive cytology to be stage IV. Parenchymal liver metastases equals stage IV.

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^aThe staging system does not distinguish between microscopic foci or replacement of tubal epithelium by malignant epithelium and grossly evident masses in the tubal lumen that do not penetrate the wall beyond the epithelium. The former have not been reported to spread beyond the tube, whereas the latter can extend beyond the tube, recur, and be fatal.

^bThe *mucosa* presumably refers to the epithelium because involvement of the lamina propria component of the mucosa requires staging of the tumor as Ia.

^cBecause the fallopian tube has no *submucosa*, this designation presumably refers to the lamina propria.

From **Berek JS, Hacker NF**, eds. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:535, with permissionxs

Radiation Therapy

Although most patients with tubal cancers have been treated with radiation therapy in the past, its role in the management of the disease is limited because of the more recent data with chemotherapy (532,533,534,535,536,537). An alternative is whole-abdominal irradiation, which has been used in patients with no evidence of gross disease in the abdomen (i.e., completely resected disease or microscopic metastases only) (3,522). Pelvic irradiation alone was once popular, but this approach should be abandoned because this disease tends to spread to the upper abdomen (523).

Prognosis

The overall 5-year survival for patients with epithelial tubal carcinomas is about 40%. This number is higher than for patients with ovarian cancer and reflects the

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somewhat higher proportion of patients diagnosed with early-stage disease. The outlook is clearly related to the stage of disease, but the available data relate to patients who have not been surgically staged. Thus, the reported 5-year survival rate for patients with stage I disease is only about 65%. The 5-year survival rate for patients with stage II disease is 50% to 60%, but it is only 10% to 20% for patients with stages III and IV disease (522,527).

Tubal Sarcomas

Tubal sarcomas, particularly malignant mixed mesodermal tumors, have been described but are rare. They occur mainly in the sixth decade and are typically advanced at the time of diagnosis. If all gross disease can be resected, platinum-based combination chemotherapy should be tried. However, survival is generally poor, and most patients die of their disease within 2 years (2,492).

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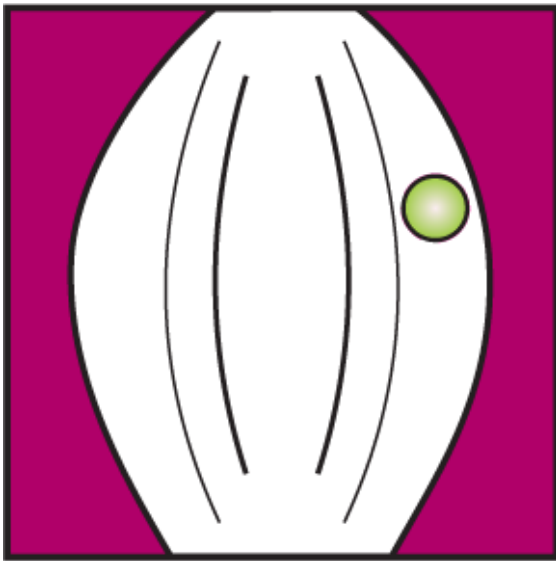
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36

Vulvar Cancer

Christine H. Holschneider

Jonathan S. Berek



- **Vulvar lesions require biopsy to avoid delay in diagnosis.**
- **The modern approach to patients with vulvar cancer is individualized.**
- **Management of the primary lesion and groin nodes is determined separately.**
- **Most T₁, T₂, and early T₃ lesions can be managed with radical local excision.**
- **Large T₃ and T₄ primary tumors are best treated with chemoradiation followed by more limited surgical resection.**
- **If groin dissection is indicated, it should be a thorough inguinofemoral lymphadenectomy.**
- **The single most important prognostic factor is lymph node status: 5-year survival with no groin node metastases is greater than 90%; with groin**

node metastases, it is 50%.

- **Recurrence in the groin is almost universally fatal.**

With 3,740 new cases and 880 deaths annually in the United States (1), vulvar cancer is uncommon, representing 3% to 5% of malignancies of the female genital tract. Squamous cell carcinomas account for about 90% of all primary vulvar malignancies, whereas melanomas, adenocarcinomas, basal cell carcinomas, and sarcomas are much less common. **The incidence of *in situ* vulvar cancer nearly doubled between the mid-1970s and the mid-1990s, whereas the overall rate of invasive squamous cell carcinoma has remained relatively stable** (2,3). However, in women younger than 50 years, there has been a striking increase in the incidence of not only *in situ* but also invasive squamous cell carcinoma of the vulva (4).

Following the reports of Taussig (5) in the United States and Way (6) in Great Britain, radical vulvectomy and *en bloc* groin dissection, with or without pelvic lymphadenectomy, has been considered standard treatment for all patients who have operable disease.

Postoperative morbidity was high and prolonged hospitalization common. **During the**

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past 20 years, a number of significant advances have been made in the management of vulvar cancer, reflecting a paradigm shift toward a more conservative surgical approach without compromised survival and with markedly decreased physical and psychological morbidity:

- **Individualization of treatment for all patients with invasive disease (7,8)**
- **Vulvar conservation for patients with unifocal tumors and an otherwise normal vulva (7,8,9,10,11)**
- **Omission of the groin dissection for patients with T₁ tumors and, 1 mm of stromal invasion (7,8)**
- **Elimination of routine pelvic lymphadenectomy (12,13,14,15,16)**
- **The use of separate incisions for the groin dissection to improve wound healing (17,18)**
- **Omission of the contralateral groin dissection in patients with lateral T₁ lesions and negative ipsilateral nodes (8,19)**
- **The use of preoperative radiation therapy to obviate the need for exenteration in patients with advanced disease (20,21)**
- **The use of postoperative radiation therapy to decrease the incidence of groin recurrence in patients with multiple positive groin nodes (16)**

Etiology

The etiology of vulvar cancer has been only partially elucidated and is likely to be multifactorial. **Based on histopathologic and environmental factors, there appear to be at least two distinct etiologic entities of squamous cell carcinoma of the vulva.**

- **Basaloid or warty types, which tend to be multifocal, occur generally in younger patients and are related to human papillomavirus (HPV) infection, vulvar intraepithelial neoplasia (VIN), and cigarette smoking.**
- **Keratinizing types, which tend to be unifocal, occur predominantly in older patients, are not related to HPV, and often are found in areas adjacent to lichen sclerosus and squamous hyperplasia.**

High-grade vulvar intraepithelial neoplasia (VIN 3) has been most closely studied as a potential precancerous lesion. The direct progression of VIN to cancer is difficult to document, but a recent review of 3,322 published patients with VIN 3, reports a 9% progression rate to cancer for untreated cases (22). Ten percent to 20% of vulvar carcinoma *in situ* lesions harbor an occult invasive component (23,24), and VIN is found adjacent to basaloid or warty vulvar squamous cell carcinomas in more than 80% of cases. DNA of HPV has been documented in 89% of patients with VIN 3 and in up to 86% of warty or basaloid type carcinomas of the vulva, but it occurs in less than 10% of the keratinizing type of carcinomas of the vulva (25).

Epidemiologic risk factors for the basaloid or warty type squamous cell carcinoma of the vulva are similar to those for cervical cancer and include a history of multiple lower genital tract neoplasias, immunosuppression, and smoking (25,26). Frequently implied as an etiologic variable for the keratinizing carcinoma is the itch–scratch cycle associated with lichen sclerosus and squamous hyperplasia,

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with atypical changes occurring in the repaired epithelium. **In keratinizing carcinoma, associated lichen sclerosus or squamous hyperplasia is found in more than 80% of patients (27,28), yet their causative role remains controversial.** Supportive evidence that some of these lesions could be precancerous comes from molecular studies that demonstrate aneuploid DNA content, *p53* overexpression, and monoclonal expansion of keratinocytes in lichen sclerosus and associated squamous hyperplasia (29,30). In the past, some studies have reported vulvar cancer to be more common in patients who are obese, have hypertension and diabetes mellitus, or are nulliparous (31,32), but a more recent case-control study of vulvar cancer was unable to confirm any of these as risk factors (26).

Types of Invasive Vulvar Cancer

The varieties of invasive vulvar cancer are shown in Table 36.1.

Table 36.1 Types of Vulvar Cancer

Type	Percent
Squamous	92
Melanoma	2-4
Basal cell	2-3
Bartholin gland (adenocarcinoma, squamous cell, transitional cell, adenoid cystic)	1
Metastatic	1
Verrucous	<1
Sarcoma	<1
Appendage (e.g., hidradenocarcinoma)	Rare

Squamous Cell Carcinoma

Approximately 90% to 92% of all invasive vulvar cancers are of the squamous cell type. As discussed previously, squamous carcinomas of the vulva can be divided into distinct histologic subtypes designated as *basaloid carcinoma*, *warty carcinoma*, and *keratinizing squamous carcinoma* (27). Mitoses are noted in these malignancies, but atypical keratinization is the histologic hallmark of invasive vulvar cancer (33). Most vulvar squamous carcinomas reveal keratinization (Fig. 36.1). Histologic features that correlate with the occurrence of inguinal lymph node metastasis are lymph-vascular space invasion, tumor thickness, depth of stromal invasion, histologic pattern of invasion (spray and stellate versus broad and pushing), and increased amount of keratin (34,35,36,37).

Microinvasive Squamous Carcinoma

Microinvasive carcinoma of the vulva has been defined as a lesion ≤ 2 cm in diameter with ≤ 1 mm stromal invasion (38). Depth of stromal invasion is measured vertically from the epithelial-stromal junction (basement membrane) of the most superficial dermal papilla to the deepest point of tumor invasion (Fig. 36.2). **When the tumor invades ≤ 1 mm, metastasis to the inguinal lymph nodes is extremely rare among reported series. However, when invasion is >1 mm, there is a significant risk of inguinal lymph node metastasis.**

Clinical Features

Squamous cell carcinoma of the vulva is predominantly a disease of postmenopausal women; the mean age at diagnosis is about 65 years. However, 15% of patients who

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develop vulvar cancer do so before age 40. There may be a long-standing history of an associated vulvar intraepithelial disorder, such as lichen sclerosus, squamous hyperplasia, or VIN. As many as 27% of patients with vulvar cancer are reported to have a second primary malignancy (39,40,41). Based on data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, patients with invasive vulvar cancer have an increased risk of 1.3 for developing a subsequent cancer. **Most of the excess second cancers were smoking related** (eg, cancers of the lung, buccal cavity and pharynx, esophagus, nasal cavity, and larynx) **or related to infection with human papillomavirus** (e.g., cervix, vulva, vagina, and anus) (42).

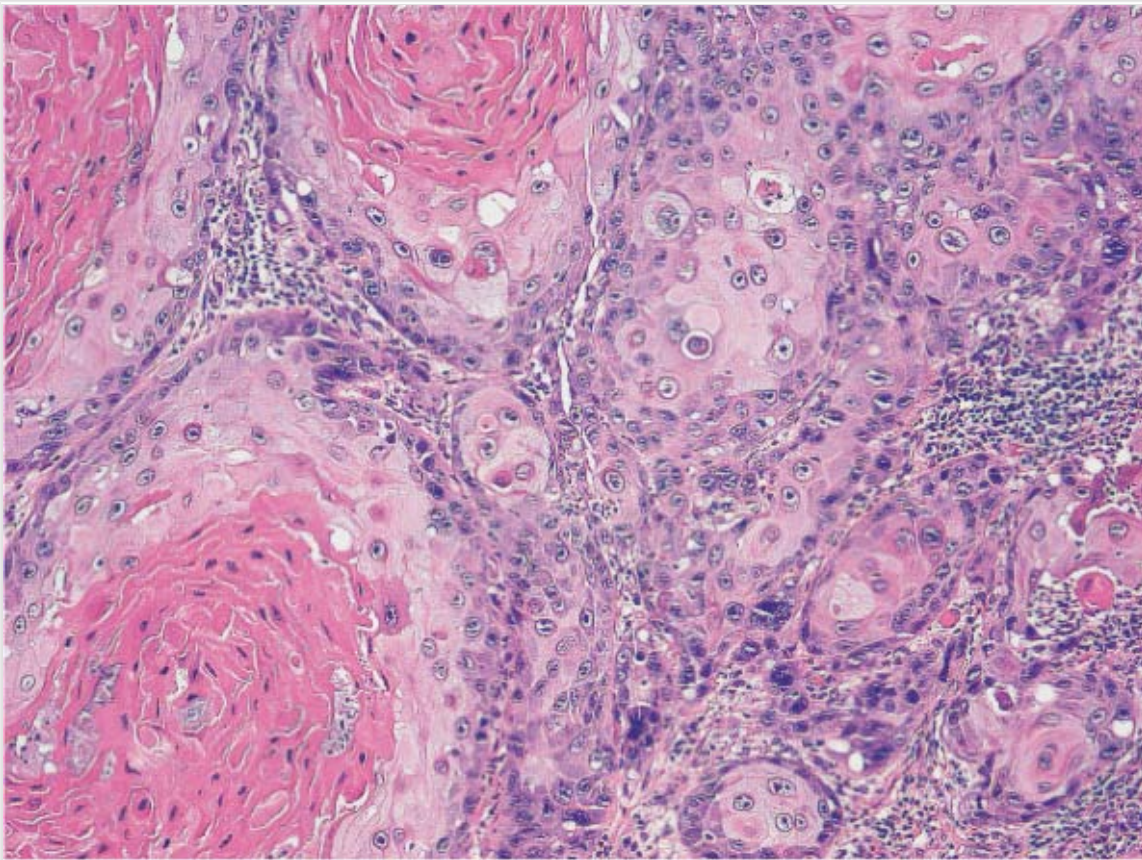


Figure 36.1 Squamous cell carcinoma of the vulva, keratinizing type. The multiple pearl formations consist of laminated keratin.

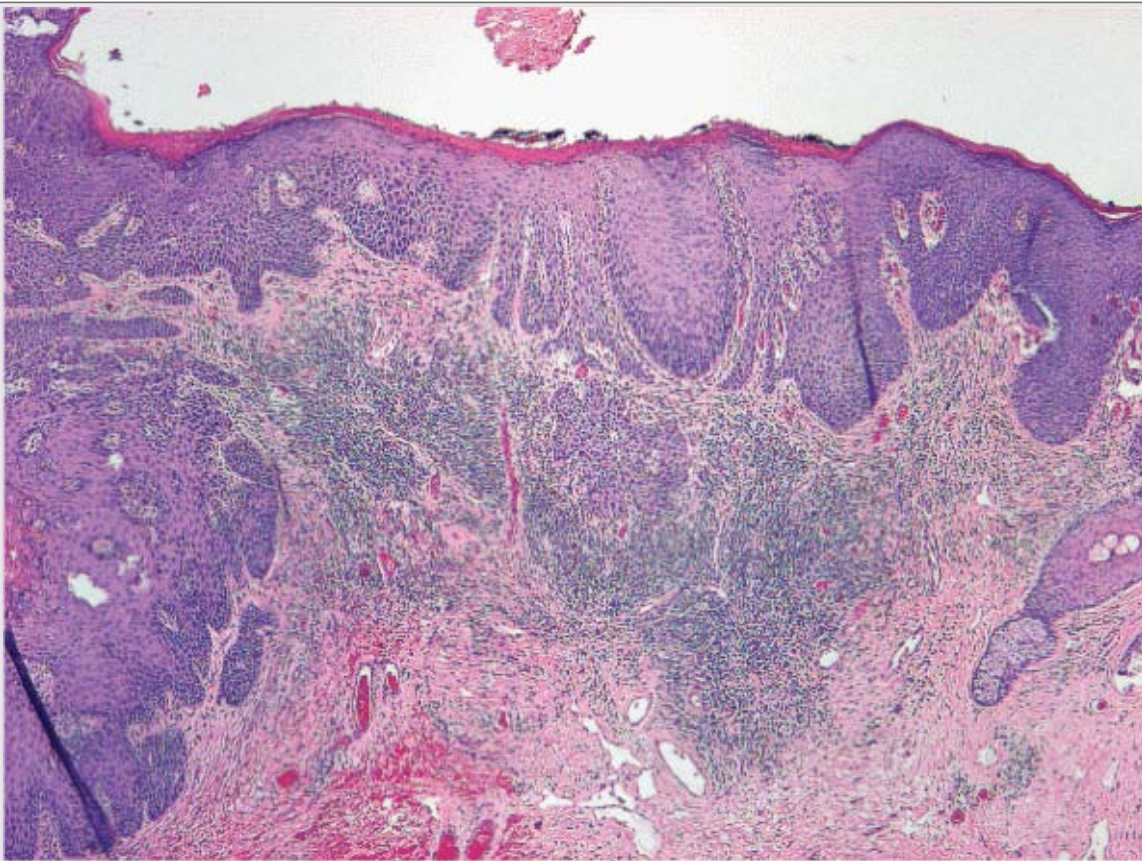


Figure 36.2 Early invasive carcinoma of vulva originating from vulvar intraepithelial neoplasia. An irregular nest of malignant cells extend from the base of rete pegs. Desmoplastic stromal reaction and chronic inflammation are useful diagnostic signs of stromal invasion. The depth of stromal invasion is measured from the base of the most superficial dermal papilla vertically to the deepest tumor cells.

Most patients are asymptomatic at the time of diagnosis. If symptoms exist, vulvar pruritus, a lump, or a mass are the most common findings. Less frequent symptoms include a bleeding or ulcerative lesion, discharge, pain, or dysuria. Occasionally, a large metastatic mass in the groin may be the initial symptom.

A careful inspection of the vulva should be part of every gynecologic examination.

On physical examination, vulvar carcinoma is usually raised and may be fleshy, ulcerated, leukoplakic, or warty in appearance. It may be pigmented, red or white, and tender or painless. The lesion may be clinically indistinct, especially in the presence of VIN or vulvar dystrophies (24). Thus, any lesion of the vulva warrants a biopsy.

Most squamous carcinomas of the vulva occur on the labia majora and minora (60%), but the clitoris (15%) and perineum (10%) also may be primary sites. Approximately 10% of the cases are too extensive to determine a site of origin, and about 5% of the cases are multifocal.

As part of the clinical evaluation, a careful assessment of the extent of the lesion, including whether it is unifocal or multifocal, should be performed. The groin lymph nodes should be evaluated carefully, and a complete pelvic examination should be performed. A cytologic sample should be taken from the cervix, and **colposcopy of the cervix and vagina should be performed because of the common association with other squamous intraepithelial or invasive neoplasms of the lower genital tract.**

Diagnosis

Diagnosis requires a wedge biopsy specimen, which usually can be obtained in the office using local anesthesia. If the lesion is only about 1 cm in diameter, excisional biopsy is preferable. The biopsy should include sufficient underlying dermis to assess for microinvasion.

Physician delay is a common problem in the diagnosis of vulvar cancer, particularly if the lesion has a warty appearance. Any confluent warty lesion requires biopsy before medical or ablative therapy is initiated.

Routes of Spread

Vulvar cancer spreads by the following routes:

- **Direct extension**, to involve adjacent structures such as the vagina, urethra, and anus
- **Lymphatic embolization** to the regional inguinal and femoral lymph nodes
- **Hematogenous spread** to distant sites, including the lungs, liver, and bone

Lymphatic metastases may occur early in the disease. Twelve percent of T₁ tumors have regional metastases (39,2). Initially, spread is usually to the inguinal lymph nodes, which are located between Camper's fascia and the fascia lata (9). From these superficial groin nodes, the disease will spread to the deep femoral nodes, which are located medially

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along the femoral vessels (Fig. 36.3). *Cloquet's* or *Rosenmüller's node*, situated beneath the inguinal ligament, is the most cephalad of the femoral node group. **Metastases to the femoral nodes without involvement of the inguinal nodes have been reported (44,45,46,47).** A recent study from the MD Anderson Cancer Center reported a 9% groin recurrence rate in 104 patients with vulvar cancer who at initial surgery had negative nodes on superficial inguinal lymphadenectomy (48), and intraoperative lymphatic mapping studies have found the sentinel node to be deep to the cribriform fascia in 5% of cases (49).

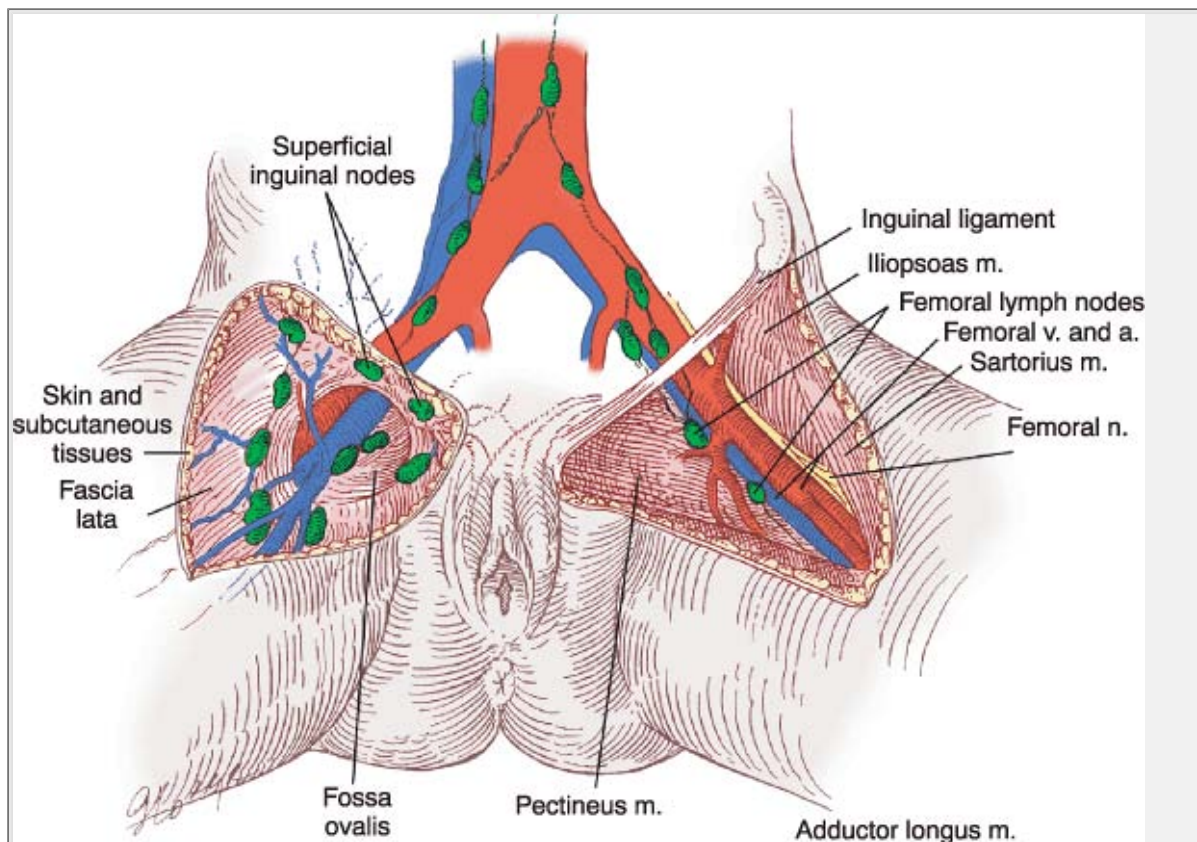


Figure 36.3 Inguinal-femoral lymph nodes. (From Berek JS, Hacker NF. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005: 548, with permission.)

From the inguinal-femoral nodes, the cancer spreads to the pelvic nodes, particularly the external iliac group. Although direct lymphatic pathways from the clitoris and Bartholin gland to the pelvic nodes have been described, these channels seem to be of minimal clinical significance (12,50,51). The lymphatics of the vulva from either side form a rich network of anastomoses along the midline. Lymphatic drainage from the clitoris, anterior labia minora, and perineum is bilateral. For lateral vulvar tumors, metastases to contralateral lymph nodes in the absence of ipsilateral nodal involvement is rare (0.4% for T₁ tumors) (43).

The overall incidence of inguinal-femoral lymph node metastases is reported to be about 30% (10,11,47,49,50,51,52,53,54) (Table 36.2). Metastases to pelvic nodes occur in about 12% of cases. Pelvic nodal metastases are rare (0.6 %) in the absence of groin

node involvement, but they occur on average in about 16% of cases with positive groin nodes (see Table 36.2). The risk increases to 33% in the presence of clinically suspicious groin nodes (13) and to about 50% if there are three or more pathologically positive inguinal-femoral nodes (13,16,40). The incidence of lymph node metastases in relation to depth of invasion is shown in Table 36.3. Hematogenous spread usually occurs late in the course of vulvar cancer and is rare in the absence of lymph node metastases.

Table 36.2 Incidence of Lymph Node Metastases in Squamous Cell Carcinoma of the Vulva

<i>Author</i>	<i>Positive Inguinal-femoral LN</i>	<i>Positive Pelvic LN/Patients with Pelvic LND</i>	<i>Positive Pelvic LN Patients with Negative Inguinal-femoral LN</i>	<i>Positive Pelvic LN/Patients with Positive Inguinal-femoral LN</i>
Rutledge et al. , 1970 (39)	33/86 (38%)	12/72 (17%)	0/53 (0%)	12/33 (36%)
Collins et al. , 1971 (52)	27/98 (28%)	11/98 (11%)	4/71 (6%)	7/27 (26%)
Morley , 1976 (53)	67/180 (37%)	6/23 (26%)	0/113 (0%)	6/67 (9%)
Krupp and Bohm , 1978 (54)	40/195 (21%)	10/195 (5%)	1/155 (0.6%)	9/40 (23%)
Benedet et al. , 1979 (55)	34/120 (28%)	4/51 (8%)	N/A	N/A
Curry et al. , 1980 (12)	57/191 (30%)	9/52 (17%)	0/134 (0%)	9/57 (16%)
Iversen et al. , 1980 (56)	90/262 (34%)	7/100 (7%)	1/172 (0.6%)	6/90 (7%)
Hacker et al. , 1983 (13)	31/113 (27%)	6/18 (33%)	0/82 (0%)	6/31 (19%)
Podratz et al. , 1983 (40)	59/175 (34%)	7/114 (6%)	0/116 (0%)	7/59 (12%)
Monaghan and Hammond , 1984 (14)	37/134 (28%)	3/80 (4%)	N/A	N/A
Hopkins et al. , 1991 (57)	61/145 (42%)	13/38 (34%)	0/84 (0%)	13/61 (21%)
Keys , 1993 (58)	203/588 (35%)	15/53 (28%)	N/A	N/A
Total	739/2,287 (32%)	103/894 (12%)	6/980 (0.6%)	75/465 (16%)

LN, lymph node; LND, lymph node dissection; N/A, data not available.

Staging

Previously, vulvar carcinoma was staged clinically based on tumor size and location, palpable regional lymph node status, and a limited search for distant metastases. The prognostic

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importance of the lymph node status is significant, yet the accuracy of the clinical assessment of the lymph nodes is limited. Microscopic metastases may be present in nodes that are not clinically suspicious, and suspicious nodes may be enlarged because of inflammation only.

When compared with surgical staging, the percentage of error in clinical staging increases from 18% for stage I disease to 44% for stage IV disease (40).

These factors led the Cancer Committee of the International Federation of Gynecology and Obstetrics (FIGO) in 1988 to introduce a surgical staging system for vulvar cancer, which was revised in 1995 to separate T₁ lesions invasive to 1 mm or less as stage Ia (Table 36.4).

This surgical staging system offers much improvement over the previous clinical staging system, but there remains need for further refinements. One major problem is that stage III represents a very heterogeneous group of patients. It includes patients ranging from those

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with a small tumor involving the distal urethra or vagina and negative nodes and those with

one microscopically involved groin node, who should have a good prognosis, to those with multiple positive groin nodes, who have a very poor prognosis.

Table 36.3 Nodal Status in T₁ Squamous Cell Carcinoma of the Vulva Versus Depth of Stromal Invasion

<i>Depth of Invasion</i>	<i>No.</i>	<i>Positive Nodes</i>	<i>Nodes</i>
< 1 mm	163	0	0
1.1–2 mm	145	11	7.7
2.1–3 mm	131	11	8.3
3.1–5 mm	101	27	26.7
> 5	38	13	34.2
Total	578	62	10.7

From **Berek JS, Hacker NF**. *Practical gynecologic oncology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2005: 549, with permission.

Table 36.4 Revised FIGO Surgical Staging for Vulvar Cancer

<i>FIGO Stage</i>	<i>TNM Classification</i>	<i>Clinical/Pathologic Findings</i>
Stage 0	Tis ^a	Carcinoma <i>in situ</i> , intraepithelial carcinoma
Stage I	T ₁ N ₀ M ₀	Tumor confined to vulva and/or perineum, ≤2 cm in greatest dimension, nodes are negative
Ia^b		Stromal invasion ≤1 mm
Ib		Stromal invasion >1 mm
Stage II	T ₂ N ₀ M ₀	Tumor confined to vulva and/or perineum, >2 cm in greatest dimension, nodes are negative
Stage III		Tumor of any size with
	T ₃ N ₀ M ₀	1. Adjacent spread to lower urethra, vagina, or anus or
	T _{1–3} N ₁ M ₀	2. Unilateral regional lymph node metastases
Stage IVa		Tumor of any size with
	T ₄ N _{any} M ₀	1. Adjacent spread to upper urethra, bladder mucosa, rectal mucosa, pelvic bone or
	T _{any} N ₂ M ₀	2. Bilateral regional lymph node metastases
IVb	T _{any} N _{any} M ₁	Any distant metastases, including pelvic lymph nodes

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumor/node/metastasis.

^a TNM Classification:			
T:	Primary tumor	N:	Regional lymph nodes
T _x :	Primary tumor cannot be assessed	Regional lymph nodes are the femoral and inguinal nodes	
T ₀ :	No evidence of primary tumor	N _x	Regional lymph nodes cannot be assessed
T _{is} :	Carcinoma <i>in situ</i> (preinvasive carcinoma)	N ₀ :	No lymph node metastases
T ₁ :	Tumor confined to the vulva and/or perineum, ≤2 cm in greatest dimension	N ₁ :	Unilateral regional lymph node metastases
		N ₂	Bilateral regional lymph node metastases
T ₂ :	Tumor confined to the vulva and/or perineum, >2 cm in greatest dimension	M	Distant metastases
		M _x	Presence of distant metastases cannot be assessed
T ₃ :	Tumor invades any of the following: lower urethra, vagina, anus	M ₀	No distant metastases
T ₄ :	Tumor invades any of the following: bladder mucosa, rectal mucosa, upper urethra, pelvic bone	M ₁	Distant metastases (including pelvic lymph node metastases)

^bThe depth of stromal invasion is measured from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
From **Beller U, Maisonneuve P, Benedet JL, et al.** Carcinoma of the vulva: FIGO 25th annual report on the results of treatment of gynecological cancer. *Int J Gynecol Obstet* 2003; 83:7–26.

Prognosis and Survival

Survival of patients with vulvar cancer correlates with FIGO stage. The prognosis for patients with early-stage disease is generally very good (Table 36.5). **The single most important prognostic factor is lymph node status** (55,56,57,58,59,60). A recent report from the Mayo Clinic on 330 patients with primary squamous cell carcinoma of the vulva demonstrated a significant correlation between lymph node status and risk of treatment failure, especially in the first 2 years after initial therapy: 44.2% overall recurrence rate with positive versus 17.5% with negative lymph nodes. Interestingly, more than one third of relapses presented 5 years or more after initial therapy (61). **Patients with negative lymph nodes have a 5-year survival rate of approximately 90%, which falls to approximately 50% for patients with positive nodes** (62). The number of positive nodes is of critical importance: **Patients with one microscopically positive lymph node have a prognosis similar to those with negative lymph nodes, whereas patients with three or more positive nodes have a poor prognosis with a two-year survival rate of 20%** (63). The survival

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rate for patients with positive pelvic nodes is about 11% (64). Histologic grade, tumor thickness, depth of stromal invasion, and lymph–vascular space involvement contribute to the risk of lymph node involvement but are not independent predictors of survival (63). Tumor ploidy is another important prognostic factor. Data from the Norwegian Radium Hospital (65) demonstrate a 5-year crude survival rate of 62% for diploid and 23% for the aneuploid tumors ($p < 0.001$). In a multivariate Cox regression analysis, tumor ploidy was the second most important prognostic factor after lymph node status.

Table 36.5 Five-year Survival for Patients with Vulvar Carcinoma

FIGO Stage	No. of Patients	Corrected 5-Year Survival (%)
I	148 (26%)	98%
II	191 (33%)	85%
III	176 (31%)	74%
IV	62 (11%)	31%
All stages	577	79%

FIGO, International Federation of Gynecology and Obstetrics.

From **Homesley HD, Bundy BN, Sedlis A, et al.** Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study). *Am J Obstet Gynecol* 1991;164:997–1003.

Treatment

After the pioneering work of Taussig (5) in the United States and Way (6) in Great Britain, *en bloc* radical vulvectomy and bilateral dissection of the groin and pelvic nodes became the standard treatment for most patients with operable vulvar cancer. If the disease involved the anus, rectovaginal septum, or proximal urethra, some type of pelvic exenteration was combined with the dissection.

Although the survival rate improved markedly with this aggressive surgical approach, several factors have led to modifications of this treatment plan during the past 30 years. These factors are summarized as follows:

- An increasing proportion of patients with early-stage disease—up to 50% of patients in many centers—have T₁ tumors.
- There were concerns about the postoperative morbidity and associated long-term hospitalization common with the *en bloc* radical dissection.
- Increasing awareness has emerged of the psychosexual consequences of radical vulvectomy.

To individualize the patient's care and determine the appropriate therapy, it is necessary to determine independently the primary lesion as well as groin lymph nodes. Before initiation of therapy, all patients should undergo colposcopy of the cervix, vagina, and vulva. Preinvasive (and rarely invasive) lesions may be present at other sites along the lower genital tract.

Management of the Primary Lesion

Early Vulvar Cancer (T₁)

The modern approach to the management of patients with T₁ carcinoma of the vulva should be individualized (7,2). There is no standard approach applicable to every

patient, and emphasis is on performing the most conservative operation that is consistent with cure of the disease. Radical vulvectomy has in

the past been considered the standard treatment for primary vulvar lesions, but this operation is associated with significant surgical morbidity and disturbances of sexual function and body image. Psychosexual sequelae are a major long-term morbidity associated with the treatment of vulvar cancer (9). One study reported that sexual arousal was reduced to the eighth percentile and body image was reduced to the fourth percentile for women who had undergone vulvectomy when compared with healthy adult women (66).

Traditionally, there has been concern that without an *en bloc* resection, intervening tissue left between the primary tumor and the regional lymph nodes may contain microscopic tumor foci in draining lymphatics. However, **experience with a separate incision technique for node dissection has confirmed that metastases rarely occur in the skin bridge in patients without clinically suspicious nodes in the groin** (18).

During the past 20 years, several investigators have advocated a radical local excision rather than a radical vulvectomy for the primary lesion for patients with T₁ tumors (7,8,9,10). Regardless of whether a radical vulvectomy or a radical local excision is performed, the surgical margins adjacent to the tumor will be the same. An analysis of the available literature indicates that the incidence of local invasive recurrence after radical local excision is not higher than that after radical vulvectomy (10,43,64,67). This finding suggests that in the presence of an otherwise normal-appearing vulva, **radical local excision is a safe surgical option, regardless of the depth of invasion**. A review of 135 patients with all stages of disease assessed the surgical margin that must be obtained to prevent local disease recurrence. In this study, a 1-cm tumor-free surgical margin on the vulvar specimen (0.8-cm on pathologic specimen) resulted in a very high rate of local control (68). Neither clinical tumor size nor the presence of coexisting benign vulvar pathology correlated with local recurrence. It is important to bear in mind that paraffin-embedded tissue shrinks by about 25%. Thus, **at the time of radical local excision, at least a 1-cm grossly negative margin, which should extend down to the level of the inferior fascia of the urogenital diaphragm, should be obtained. For stage Ia lesions, lesser forms of vulvar excision, such as wide local excision, are as effective as radical surgery for the prevention of vulvar recurrences** (69).

When vulvar cancer arises in the presence of VIN or some nonneoplastic epithelial disorder, treatment will be influenced by the patient's age. Elderly patients who often have had many years of chronic itching may not be disturbed by the prospect of a vulvectomy. In younger women, it will be desirable to conserve as much of the vulva as possible. Thus, radical local excision should be performed for the invasive disease, and the associated intraepithelial disease should be treated in the manner most appropriate to the patient. For example, topical steroids may be required for lichen sclerosus or squamous hyperplasia, whereas VIN may require superficial local excision and primary closure.

Radical local excision is most appropriate for lesions on the lateral or posterior aspects of the vulva (Fig. 36.4). Midline lesions pose special challenges because of their proximity to clitoris, urethra, or anus. For anterior lesions, conservative clitoris-sparing surgery allows for excellent local control as long as pathological margins are at least 8 mm (70). For tumors that involve the clitoris or that are in close proximity to it, any type of surgical excision will have psychosexual consequences. In addition, marked edema of the posterior vulva may occur. For young patients with periclitoral lesions, the primary lesion can be treated with a small field of radiation therapy, possibly with concomitant sensitizing chemotherapy. Small vulvar lesions should respond very well to about 5,000 cGy external radiation, and biopsy can be

performed after therapy to confirm the absence of any residual disease (62).



Figure 36.4 Small (T_1) vulvar carcinoma at the posterior fourchette. (From Berek JS, Hacker NF. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2005:554, with permission.)

T₂ and T₃ Vulvar Cancer

In recent years, the indications for vulvar conservation have been extended to selected patients with T_2 and early T_3 tumors. Although the reported experience is limited (10,11,71), **a recent study suggests that the local recurrence rate for patients with conservatively treated T_2 tumors is identical to that for patients with T_1 tumors (72) as long as surgical margins of at least 1 cm are obtained.** The tumor-free margin should be the same, whether or not a radical vulvectomy or a radical local excision is performed, so it would be seem to be

both feasible and desirable to extend the indications for vulvar conservation, particularly for younger patients. **Tumors that are most suitable to a more conservative resection are those involving the posterior half of the vulva, where preservation of the clitoris and mons pubis is feasible.**

For patients with more advanced T₂ and T₃ lesions, management consists of radical vulvectomy and bilateral inguinal-femoral lymphadenectomy or chemoradiation therapy, as discussed below. If the disease involves the distal urethra, vagina, or anus, partial resection

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of these organs would be required. Alternatively, it is often preferable to give preoperative radiation therapy with chemosensitization to allow for a less radical resection (see below).

Closure of Large Defects

After radical local excision, primary closure without tension often can be accomplished for smaller defects. However, if a more extensive dissection has been required to treat a large primary lesion, a number of options are available to repair the defect.

- An area may be left open to granulate, which it will usually do over a period of 6 to 8 weeks (73).
- Full-thickness skin flaps may be devised (74,75,76,77). The rhomboid flap is best suited to covering large defects of the posterior vulva (77), whereas for lateral defects, a mons pubis pedicle flap has been advocated (74).
- Myocutaneous flaps may be developed to cover the defect. Unilateral or bilateral gracilis myocutaneous grafts are most useful when an extensive area from the mons pubis to the perianal area has been resected. Because the graft brings a new blood supply to the area, it is particularly applicable if the vulva is poorly vascularized from prior surgical resection or radiation (78).
- If extensive defects exist in the groin and vulva, the tensor fascia lata myocutaneous graft may be the most applicable (79).

Advanced Disease: Large T₃ and T₄ Primary Tumors

To achieve primary surgical clearance for tumors involving the upper urethra, anus, rectum, or rectovaginal septum, pelvic exenteration would be needed in addition to radical vulvectomy and inguinal-femoral lymphadenectomy, which carries an extremely high physical and psychological morbidity (66,2). Reported 5-year survival rates are about 50% (81,82,83,84). For many of these patients, a combined approach of surgery and radiation therapy offers improved survival and reduced morbidity and thus becomes the preferred treatment approach. Numerous small prospective and retrospective series report on the use of external beam radiation, often with concomitant chemotherapy to shrink the primary tumor. Reported initial response rates to chemoradiation approximate 90% (85,86,87,88). **It is important that this chemoradiation is followed by a more limited resection of the tumor bed and lymphadenectomy on an individualized basis.** About one half of the specimens will contain residual tumor (21,2), and local relapse rates are as high as 50% to 79% with

external radiation alone (with or without concomitant chemotherapy) (90,2), emphasizing the need for a combined approach that involves radiation and surgery.

As experience with this combination therapy has evolved, it appears that **external beam therapy is generally appropriate for most cases, with more selective use of brachytherapy. The extensiveness of the surgery has also been significantly modified. A more limited vulvar resection is now advocated, and bulky N₂ and N₃ nodes are resected without full groin lymphadenectomy to avoid the leg edema associated with groin lymphadenectomy and radiation. With this combined radiation-surgical approach, 5-year survival rates as high as 76% have been reported (89).** With the experience now accrued, preoperative radiation, with or without concurrent chemotherapy, should be regarded as the treatment of first choice for patients with advanced vulvar cancer who would otherwise require some type of pelvic exenteration.

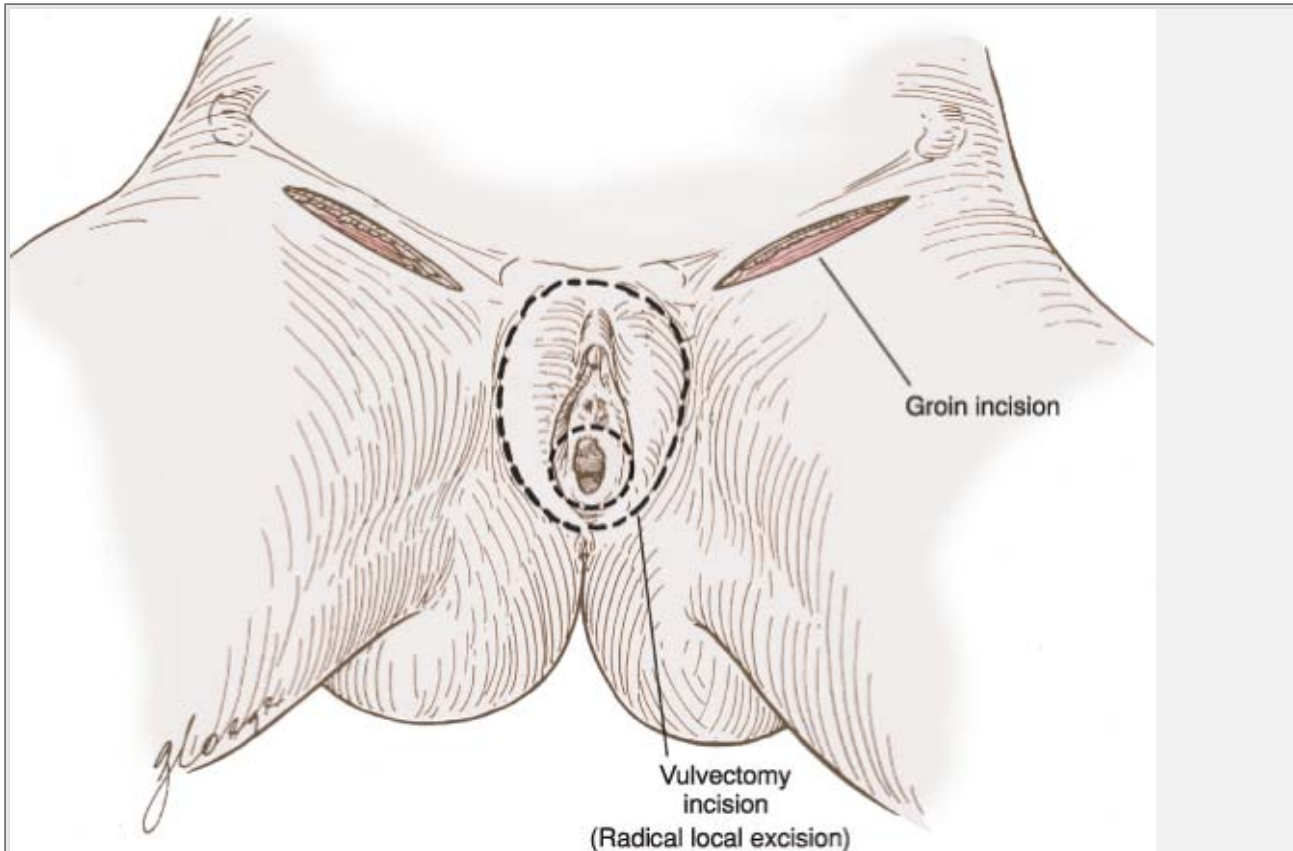


Figure 36.5 Skin incision for groin dissection through a separate incision. A line is drawn 1 cm below and parallel to the groin crease, and a narrow ellipse of skin is removed. Radical local excision which would be appropriate for patient in Figure 36.4. (Revised from **Berek JS, Hacker NF. Practical gynecologic oncology**, 2nd ed. Baltimore, MD: Williams & Wilkins, 1994, p. 418. with permission.)

Management of the Lymph Nodes

Groin dissection is associated with postoperative wound infection and breakdown, as well as chronic leg edema. Although the incidence of wound breakdown is reduced significantly

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when separate incisions are used for the groin dissection (Fig. 36.5) (18), chronic leg edema remains a major problem. When assessing a patient for groin dissection, the following three facts should be kept in mind:

- The only patients with virtually no risk of lymph node metastases are those whose tumor invades the stroma to <1 mm.
- Patients who develop recurrent disease in an undissected groin have a >90% mortality (92).
- Based on the laterality of the vulvar lesions, an ipsilateral or bilateral lymphadenectomy becomes necessary.

Appropriate groin dissection is the single most important factor in decreasing the mortality for early vulvar cancer.

Microinvasive Carcinoma

All patients whose tumors demonstrate more than 1 mm of stromal invasion require inguinal-femoral lymphadenectomy. A wedge biopsy specimen of the primary tumor should be obtained, and the depth of invasion should be determined. If it is smaller than 1 mm on the wedge biopsy specimen, the entire lesion should be locally excised and analyzed histologically to determine the depth of invasion. If there is still no invasive focus larger than 1 mm, groin dissection may be omitted provided there is no lymph-vascular space invasion and there are no clinically suspicious groin lymph nodes. Although an occasional patient with less than 1 mm of stromal invasion has had documented groin node metastases (93), the incidence is so low that it is of no practical significance.

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Inguinal-femoral Lymphadenectomy

If groin dissection is indicated in patients with early vulvar cancer, it should be a thorough inguinal-femoral lymphadenectomy. The GOG reported six groin recurrences among 121 patients with T₁ N₀ tumors after a superficial (inguinal) dissection, even though the removed inguinal nodes were negative (47), and a recent study from the MD Anderson Cancer Center reported a 9% groin recurrence rate in 104 patients with vulvar cancer and negative nodes on superficial inguinal lymphadenectomy (48). Whether all of these recurrences were in the femoral nodes is unclear, but both studies indicate that an incomplete groin dissection will increase the number of groin recurrences and, therefore, mortality. Furthermore, GOG data indicate that radiation therapy cannot substitute for groin dissection followed by selective radiation as indicated, even in patients with clinically nonsuspicious lymph nodes (94). This GOG study was closed early because a significantly higher incidence of recurrences occurred in women who were receiving groin radiation therapy only (19% versus 0%). The dose of radiation was 5,000 cGy given in daily 200-cGy fractions to a depth of 3 cm below the anterior skin surface. Although the radiation regimen prescribed has been criticized extensively, the therapeutic effects of an alternative radiation regimen remain to be determined.

Unilateral Versus Bilateral Groin Dissection

It is clear that it is not necessary to perform a bilateral groin dissection if the primary lesion is unilateral and the ipsilateral lymph nodes are negative. In a patient with unilateral T₁ lesion and negative ipsilateral groin nodes, the risk of contralateral lymph node metastasis is 0.4% (43). However, there is an increase in the risk of contralateral

nodal involvement proportional to the number of positive ipsilateral inguinal nodes (16). Thus, **it is recommended that patients with any bulky or multiple microscopically positive ipsilateral groin lymph nodes undergo contralateral inguinal-femoral lymphadenectomy as well. Bilateral inguinal-femoral lymphadenectomy should be performed for midline lesions (clitoris, anterior labia minora, posterior fourchette) or those within 2 cm of the midline because of the more frequent contralateral lymph flow from these regions (95).**

Management of Pelvic Lymph Nodes

In the past, pelvic lymphadenectomy has been considered part of the routine surgery for invasive vulvar cancer. However, the incidence of pelvic lymph node metastasis is rare in the absence of groin node involvement (see Table 36.2), thus a more selective approach is preferred. Patients most prone to pelvic lymph node metastasis are those with clinically suspicious or three or more pathologically positive groin nodes (12,13,15,40). In these patients, the pelvis requires treatment by pelvic lymphadenectomy or radiation. **If a preoperative pelvic imaging study reveals enlarged pelvic lymph nodes, resection of these nodes should be performed via an extraperitoneal approach because of the inability of external beam radiation therapy to sterilize bulky positive pelvic nodes.**

Sentinel Lymph Node Studies

A number of investigators have explored the use of intraoperative lymphatic mapping using lymphoscintigraphy with technetium-99m-labeled nanocolloid or isosulfan blue dye to identify a sentinel node that would predict the presence or absence of regional nodal metastases (49,96,97,98). A recent systematic review of 29 mostly small studies published to date of 961 groins found lymphoscintigraphy to be the most accurate technique with a pooled sensitivity and negative likelihood ratio of 97% and 0.12, respectively (99). **These preliminary studies suggest that a sentinel node can be identified in most patients (100).** The sensitivity of the sentinel node assessment may be further enhanced by ultrastaging using serial sectioning or immunohistochemistry to detect micrometastases (101,102,103). Reliable identification of the sentinel node and foregoing a full lymphadenectomy in patients with clinically nonsuspicious groin lymph nodes and a negative sentinel node may significantly reduce the number of patients who undergo unnecessary, extensive lymphadenectomy in the absence of disease. Intraoperative lymphatic mapping and sentinel node identification is currently being evaluated by the Gynecologic Oncology Group in a large multi-institutional

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study (GOG 173), and the European Organization for Research and Treatment of Cancer is performing an intergroup randomized controlled trial of sentinel node versus full inguinofemoral lymphadenectomy (EORTC 55001). **Until these trials document the accuracy of the negative predictive value of an uninvolved sentinel node, complete inguinal-femoral lymphadenectomy remains indicated in all but stage Ia disease, given the high mortality of recurrence in an undissected groin.**

Postoperative Management

Despite the age and general medical condition of many elderly patients with vulvar cancer, surgery is usually remarkably well tolerated. Patients should be able to commence eating a low-residue diet on the first postoperative day. In the past, bed rest had been advised for 3 to 5 days postoperatively to allow for immobilization of the wounds and foster healing.

Because radical local excisions are being performed with increasing frequency and

groin lymphadenectomy are done through separate incisions, patients generally begin ambulation on postoperative day 1 or 2. Pneumatic calf compression or subcutaneous heparin should be given to help prevent deep venous thrombosis, and active leg movements are to be encouraged. Frequent dressing changes are performed to keep the vulvar wound dry. Meticulous perineal hygiene is maintained. Suction drainage of each side of the groin is continued until output is minimal to help decrease the incidence of groin seromas. It is not uncommon for suction drainage to continue for 10 or more days. The Foley catheter is removed once the patient is ambulatory. If there is significant periurethral swelling, prolonged bladder drainage may be advisable. If there is breakdown of the vulvar wound, sitz baths or whirlpool therapy is helpful, followed by drying of the perineum with a hair dryer.

Early Postoperative Complications

The major immediate morbidity is related to groin wound infection, necrosis, and breakdown. This complication has been reported in as many as 53% to 85% of patients having an *en bloc* operation (39,2). **With the separate-incision approach**, the incidence of wound breakdown can be reduced to about 44%; **major breakdown occurs in about 14% of patients** (18,41,104). With appropriate antibiotics, debridement, and wound dressings, the area will granulate and re-epithelialize over the next several weeks and may be managed with home nursing. Whirlpool therapy is effective for areas of extensive breakdown.

Other early postoperative complications include urinary tract infection, seromas in the femoral triangle, deep venous thrombosis, pulmonary embolism, myocardial infarction, hemorrhage, and, rarely, osteitis pubis. Lymphocysts or groin seromas occur in about 10% to 15% of cases and should be managed by periodic sterile aspiration. Anesthesia of the anterior thigh resulting from femoral nerve injury is common and usually resolves slowly.

Late Complications

One major late complication is chronic lymphedema, which occurs on average in about 30% of patients (39,40,41,104,105). Recurrent lymphangitis or cellulitis of the leg develops in about 10% of patients and usually responds to oral antibiotics. Urinary stress incontinence, with or without genital prolapse, occurs in about 10% of patients after radical vulvectomy and may require corrective surgery. Introital stenosis can lead to dyspareunia and may require a vertical relaxing incision, which is sutured transversely. An uncommon late complication is femoral hernia, which usually can be prevented intraoperatively by closure of the femoral canal with a suture from the inguinal ligament to Cooper's ligament. Pubic osteomyelitis and rectovaginal or rectoperineal fistulas are rare late complications.

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Other major long-term treatment complications associated with the extent of vulvar surgery include depression, altered body image, and sexual dysfunction (66,2). Modifications in the radical extent of the surgical approach and appropriate preoperative and postoperative counseling may help lessen some of the psychological trauma.

Role of Radiation Therapy

Radiation therapy traditionally has been considered to have a limited role in the management of patients with vulvar cancer. In the orthovoltage era, local tissue tolerance was poor and vulvar necrosis was common, but with megavoltage therapy, tolerance has improved significantly. Thus, radiation therapy, frequently with concurrent chemotherapy, is gaining

an increasingly important role in the management of patients with vulvar cancer. It is important to remember, though, that with a rare exception, radiation therapy alone has little place in the primary management of vulvar cancer. It is generally indicated in conjunction with surgery.

The indications for radiation therapy for patients with primary vulvar cancer are still evolving.

At present, radiation seems to be clearly indicated in the following situations:

- **Preoperatively, in patients with advanced disease who would otherwise require pelvic exenteration (20,2) or suffer loss of anal or urethral sphincteric function**
- **Postoperatively, to treat the pelvic lymph nodes and groin of patients with two or more microscopically positive or one grossly positive groin node (16)**

Possible roles for radiation therapy include the following:

- Postoperatively, to help prevent local recurrences in patients with involved or close surgical margins (106,107,108)
- As primary therapy for patients with small primary tumors, particularly clitoral or periclitoral lesions in young and middle-aged women, for whom surgical resection would have significant psychological consequences (62)

No additional treatment is recommended if one microscopically positive groin node is found. The prognosis for this group of patients is excellent (13), and only careful observation is required. Even if an unilateral groin dissection has been performed for a lateral lesion, there seems to be no indication for dissection of the other side, because contralateral lymph node involvement is likely only if there are multiple microscopic or any gross ipsilateral inguinal node metastases (13,2).

If clinically evident groin metastases or two or more microscopically positive groin nodes are found, which is unusual in patients with T₁ vulvar cancer, the patient is at increased risk of groin and pelvic recurrence and should receive postoperative groin and pelvic irradiation. In 1977, the GOG initiated a prospective trial in which patients with positive groin nodes were randomized to either ipsilateral pelvic node dissection or bilateral pelvic node dissection plus groin irradiation (16). Radiation therapy consisted of 4,500 to 5,000 cGy to the midplane of the pelvis at a rate of 180 to 200 cGy per day. The survival rate for the radiation group (68% at 2 years) was significantly better than the survival rate for the pelvic lymphadenectomy group (54% at 2 years) ($p = 0.03$). The survival advantage was limited to patients with clinically evident groin nodes or more than one microscopically positive groin node. Groin recurrence occurred in 3 of 59 patients (5%) treated with radiation, compared with 13 of 55 (23.6%) patients treated with lymphadenectomy ($p = 0.02$). Four patients who received radiation had a pelvic recurrence, compared with one who had lymphadenectomy. These data indicate no benefit from

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pelvic irradiation compared with pelvic lymphadenectomy for the prevention of pelvic recurrence, but they do highlight the value of prophylactic groin irradiation in preventing groin recurrence in patients with multiple positive groin nodes.

Recurrent Vulvar Cancer

Approximately two thirds of recurrences of vulvar cancer occur within the first 2 years from initial therapy (109), with groin recurrences occurring sooner (median time to recurrence 6 months) than vulvar recurrences (median time to recurrence 3 years) (110).

Recurrence of vulvar cancer correlates most closely with the number of positive groin nodes (13). Patients with fewer than three positive nodes, particularly if the nodes are only microscopically involved, have a low incidence of recurrence at any site, whereas patients with three or more positive nodes have a high incidence of local, regional, and systemic recurrences (13,2).

Local Recurrence

Margin status at the time of radical resection of the vulvar cancer is the most powerful predictor of local vulvar recurrence, with an almost 50% recurrence risk with margins closer than 0.8 cm (68). Margin status does not, however, predict survival (60). Local vulvar recurrences are likely in patients with primary lesions larger than 4 cm in diameter, especially if lymph-vascular space invasion is present (106,2) and in patients with deeply invasive tumors (112). When detected early, isolated local failure is usually salvageable by additional surgical therapy (10,18,41,47,113), often with a gracilis myocutaneous graft to cover the defect. Radiation therapy, particularly a combination of external beam therapy plus interstitial needles, at times combined with chemotherapy, has also been used to treat vulvar recurrences (114). One study reported on 10 patients treated in this manner, nine of whom were still alive with a mean follow-up of 28 months (115). However, 6 of the 10 patients developed severe radionecrosis at a median of 8.5 months after radiation, and the authors concluded that although this treatment was highly effective, it also had a high degree of morbidity.

Regional and Distant Recurrence

Regional and distant recurrences are difficult to manage and are associated with a poor prognosis (106,109,110). Radiation therapy may be used in conjunction with surgery for groin recurrence, whereas chemotherapeutic agents that have activity against squamous carcinomas may be offered for distant metastases. The literature on the use of chemotherapy for recurrent vulvar cancer consists of mainly small series. The most extensively studied regimens contain *bleomycin* and *methotrexate*, with or without *cisplatin* or *CCNU* (a nitrosourea) and *bleomycin* and *mitomycin C* (116,2), but response rates are low and the duration of response is usually disappointing. Long-term survival is very uncommon with regional or distant recurrence.



Figure 36.6 Melanoma of the vulva involving the right labium minus. (From Hacker NF, Moore JG, Gambone JC. Essentials of obstetrics and gynecology. In: Berek JS, Hacker NF. Practical gynecologic oncology, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:473, with permission.)

Melanoma

Vulvar melanomas are rare, with an incidence of 0.1 to 0.19 per 100,000 women (118,2). They account for 4% to 10% of all cases and are the second most common form of vulvar malignancy (38). Most melanomas arise *de novo* (120), but they may arise from a pre-existing junctional nevus. Vulvar melanomas occur predominantly in postmenopausal white women. The incidence of cutaneous melanomas worldwide is increasing significantly. Vulvar melanomas appear to behave in a manner similar to that of other cutaneous melanomas (121,122,123).

Most patients with vulvar melanoma have no symptoms except for a pigmented lesion that may be enlarging. Some patients have itching or bleeding, and a few have a groin mass. Vulvar melanomas occur most frequently on the labia minora or the clitoris (Fig. 36.6),

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and extension into the urethra or vagina at discovery is not uncommon. Any pigmented lesion on the vulva should be excised or, if the lesion is large, sampled for biopsy unless it is known to have been present and unchanged for some years. Most vulvar nevi are junctional and may be precursor lesions to melanoma; thus, any nevus of the vulva should be removed.

Histopathology

There are three basic histologic types of vulvar melanoma (Fig. 36.7).

The *mucosal lentiginous melanoma* is a flat freckle that may become quite extensive but tends

to remain superficial.

- The *superficial spreading melanoma* tends to remain relatively superficial early in its development.
- The *nodular melanoma*, which is the most aggressive, is characterized by a raised lesion that penetrates deeply and may metastasize widely.

In the largest series reported to date, more than one fourth of the cases of melanomas were macroscopically amelanotic (118). Vulvar melanoma tends to spread early, not only lymphatically but also hematogenously.

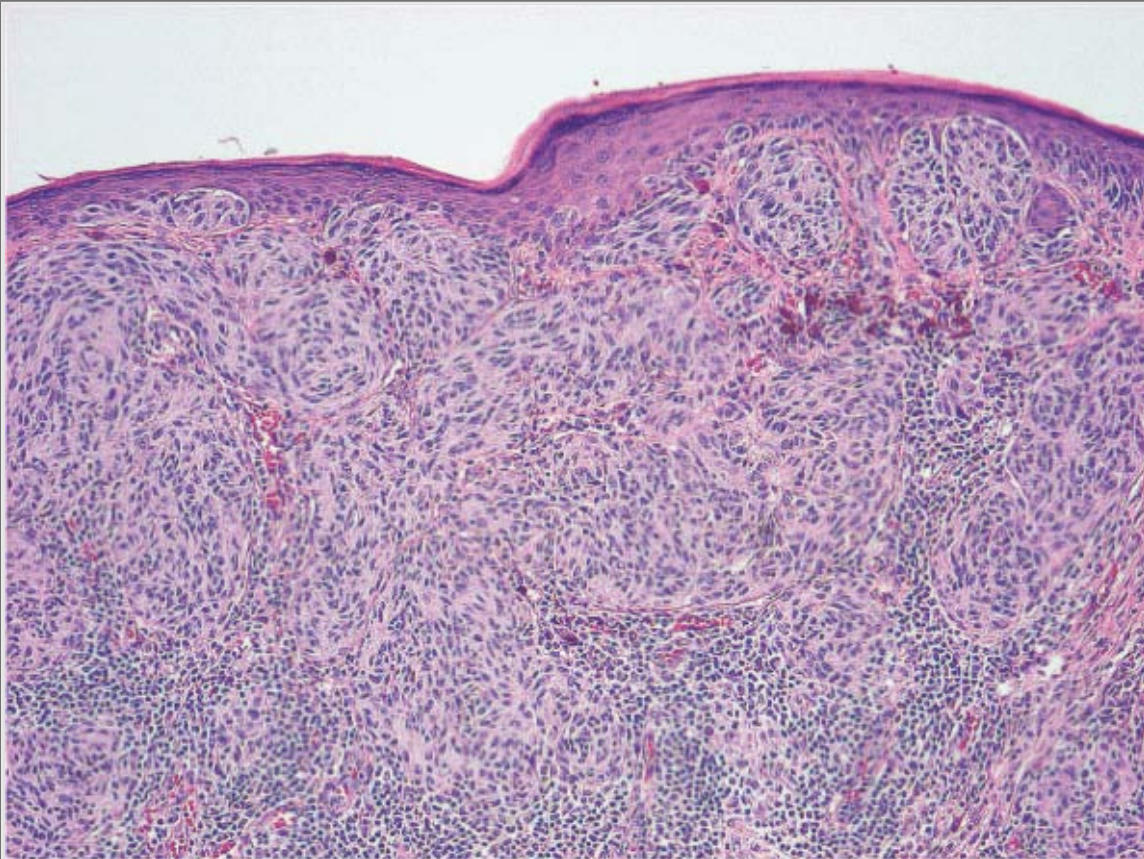


Figure 36.7 Vulvar melanoma. Spindle-shaped melanoma cells form interlacing bundles, and some contain melanin pigment (right upper corner). Epidermal invasion is evident in the form of Pagetoid migration (left upper corner).

Staging

The FIGO staging used for squamous lesions is not applicable to melanomas because the lesions are usually much smaller and the prognosis is related to the depth of tumor invasion rather than to the diameter of the lesion (121,124,125). The leveling system established by Clark et al. (125) for cutaneous melanomas is less readily applicable to vulvar lesions because of the different skin morphology. The vulvar skin

lacks a well-defined papillary dermis. Breslow (126) measured the thickest portion of the melanoma from the surface of intact epithelium to the deepest point of invasion. This system is more adequate for the vulva. Chung et al. (124) proposed a modified system that retained

Clark's definitions for levels I and V but arbitrarily defined levels II, III, and IV, using measurements in millimeters. A comparison of these systems is shown in Table 36.6.

	Clark Level (125)	Chung Depth of Invasion (124)	Breslow Tumor Thickness (126)
I	Intraepithelial	Intraepithelial	<0.76 mm
II	Into papillary dermis	<1 mm from granular layer	0.76–1.5 mm Superficial invasion
III	Filling dermal papillae	1.1–2.0 mm from granular layer	1.51–2.25 mm Intermediate invasion
IV	Into reticular dermis	>2 mm from granular layer	2.26–3.0 Intermediate invasion
V	Into subcutaneous fat	Into subcutaneous fat	>3 mm Deep invasion

The revised 2002 American Joint Committee on Cancer (AJCC) staging for cutaneous melanoma replaced the Clark level of invasion by tumor thickness and included other important prognostic factors, such as primary tumor ulceration, number of metastatic lymph nodes, micrometastatic disease based on sentinel lymph node biopsy or elective node dissection, the site(s) of distant metastatic disease, and serum LDH levels (127).

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Treatment

With better understanding of the prognostic significance of the microstage, some individualization of treatment has developed. However, treatment of vulvar melanoma continues to be controversial, in part because of the lack of large retrospective studies, which makes it difficult to draw conclusions regarding its behavior and best treatment. Currently used treatments are guided by experience from cutaneous melanoma in general and squamous cell carcinomas of the vulva. Paralleling the trend toward more conservative surgical management of cutaneous melanoma, there is a shift toward more conservative management of vulvar melanoma (122,123,128,129).

It is generally accepted that lesions with less than 1 mm of invasion may be treated with radical local excision alone (124,2). With more invasive lesions, *en bloc* resection of the primary tumor and regional groin nodes has traditionally been recommended. In the last 15 years, however, **radical vulvectomy has been performed less frequently, and survival does not seem to be compromised** (131). One study reported on 32 patients with vulvar melanoma who underwent local excision ($n = 14$), simple vulvectomy ($n = 7$), or radical resection ($n = 11$) (132). No group had a superior survival rate, although the overall survival rate at 5 years was only 25%. More recently, another study reported on 59 patients who underwent radical vulvectomy and 19 who underwent more conservative resections (122). Survival was not improved by the more radical approach, and they recommended radical local excision for the primary tumor, with groin dissection for tumors with a thickness of more than 1 mm. Current literature on cutaneous melanoma suggests that a 1-cm margin of skin and subcutaneous tissue is sufficient for the treatment of superficial localized melanoma (Breslow tumor thickness <0.76 mm), whereas a 2-cm margin suffices for intermediate-thickness lesions (1 to 4 mm) (133,2). Because melanomas commonly involve the clitoris and labia minora, the vaginourethral margin of resection is a common site of failure, and care should

be taken to obtain an adequate "inner" resection margin (135). A 10-year survival rate of 61% has been shown for lateral lesions, compared with 37% for medial lesions ($p = 0.027$) (111).

Controversy exists as to which patients may benefit from inguinal-

femoral lymphadenectomy. A prospective study by the GOG demonstrated that the risk of inguinal-femoral lymph node metastasis correlated with the Breslow microstage (123). As with cutaneous melanoma, it appears that for superficial lesions (Breslow tumor thickness <0.76 mm), the risk for nodal spread is so low that routine lymphadenectomy is not indicated as long as the nodes appear clinically to be free of disease. **For intermediate-thickness (1 to 4 mm) cutaneous melanoma, a randomized controlled trial of elective lymph node dissection versus observation showed a 5-year survival advantage for patients who underwent elective lymph node dissection, who were younger than 60 years, and whose tumors were characterized by 1- to 2-mm thickness and no ulcerations (136). Patients with deeply invasive cutaneous melanomas (>4-mm tumor thickness) have a high risk of regional and systemic metastases and are unlikely to benefit from regional lymphadenectomy (137).** Given some of the epidemiologic, histologic, and prognostic differences between vulvar and cutaneous melanoma (138), extrapolation of these data to the vulva should be done with caution. Specific to patients with vulvar melanoma, there is a small body of literature to suggest that there may be a clinical benefit in elective groin lymphadenectomy and the resection of clinically positive nodes (121,2).

Table 36.7 Prognosis for Patients with Vulvar Melanoma Stratified by Breslow Microstaging

<i>Breslow Tumor Thickness</i>	<i>No. of Patients</i>	<i>% DOD</i>
< 0.76 mm	31 [19]	7 (23%) [1 (5%)] ^a
0.76–1.5 mm	35	6 (17%)
1.51–3.0 mm	42	23 (55%)
> 3.0 mm	195	131 (67%)

DOD, died of disease.

^aAll but one of these seven deaths were reported in one study with an unusually low 5-year survival of 48% for 12 patients with superficial melanomas of Breslow thickness <0.76 mm. If these 12 cases were excluded, 5% of patients with superficial melanoma of the vulva died of disease.

From references 118, 122, 130, 139, 140, 148–151.

Pelvic node metastases do not occur in the absence of groin node

metastases (135,139,140). In addition, the prognosis for patients with positive pelvic nodes is so poor that there seems to be no value in performing pelvic lymphadenectomy for this disease. Immunotherapy and chemotherapy have demonstrated modest results in cutaneous melanoma. Several randomized cooperative and intergroup trials of high-risk melanoma patients have demonstrated a small but significant improvement in disease-free and overall

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survival with adjuvant interferon alpha (141,142,143). Dacarbazine (DTIC) is considered the most active single-agent chemotherapy with a response rate of 16%, and randomized controlled trials have failed to date to demonstrate superiority of any multiagent regimen (144). Targeted therapy is an area of promising development as single agents, in combination, and combined with chemotherapy. Vaccines stimulating both antibody and T-cell responses against melanoma are a promising but still considered experimental treatment that is under investigation (145). Radiation has a role in the palliative management of brain metastasis and symptomatic bony metastases. Estrogen receptors have been demonstrated in

human melanomas, and an occasional response to *tamoxifen* has been reported (146,2).

Prognosis

The behavior of melanomas can be quite unpredictable, but the overall prognosis is poor. The reported 5-year survival rate for vulvar melanoma ranges from 25% (132) to 50% (118,2). Because vulvar melanoma has a propensity for late recurrences, 5-year survival may not reflect cure. Prognosis is best predicted by microstaging. Patients with lesions invading to 1 mm or less have a good prognosis, but as depth of invasion increases, the prognosis worsens (Table 36.7). Tumor volume has been reported to correlate with prognosis; patients whose lesions have a volume less than 100 mm³ have an excellent prognosis (140). Additional prognostic factors are the patient's age, AJCC stage, presence of multifocal or satellite lesions, tumor ulceration, central tumor location, histologic growth pattern, lymph-vascular space involvement, and aneuploidy (118,121,122,123,149).

Bartholin Gland Carcinoma

Epidemiology

Primary carcinoma of the Bartholin gland is a rare form of vulvar cancer, which accounts for about 2% to 7% of vulvar malignancies (152). Because of its rarity, individual experience with the tumor is limited, and recommendations for management must be based on the review of small published series. To date, only about 300 cases have been reported (50,152,153). Bartholin gland carcinoma is 5 times more common in postmenopausal than in premenopausal women (154).

Histopathology

The bilateral Bartholin glands are greater vestibular glands situated posterolaterally in the vulva. Their main duct is lined with stratified squamous epithelium, which changes to transitional epithelium as the terminal ducts are reached. Because tumors may arise from the

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gland or the duct, a variety of histologic types occur, including adenocarcinomas, squamous carcinomas, and, rarely, transitional cell, adenosquamous, and adenoid cystic carcinomas.

Classification of a vulvar tumor as a Bartholin gland carcinoma has typically required that it fulfill Honan's criteria, which are as follows:

- **The tumor is in the correct anatomic position.**
- **The tumor is located deep in the labium majus.**
- **The overlying skin is intact.**
- **There is some recognizable normal gland present.**

Strict adherence to these criteria will result in underdiagnosis of some cases. Large tumors may ulcerate through the overlying skin and obliterate the residual normal gland. Although transition between normal and malignant tissue is the best criterion, some cases will be

diagnosed on the basis of their histologic characteristics and anatomic location.

Signs and Symptoms

The most common initial symptom of Bartholin gland carcinoma is a vulvar mass or perineal pain. About 10% of patients have a history of inflammation of the Bartholin gland, and malignancies may be mistaken for benign cysts or abscesses. Therefore, delay of diagnosis is common, particularly for premenopausal patients. The differential diagnosis of any pararectovaginal neoplasm should include cloacogenic carcinoma and secondary neoplasm (153).

Treatment

Traditionally, treatment has been radical vulvectomy with bilateral groin and pelvic node dissection (155). However, there seems to be **no indication for dissection of the pelvic nodes in the absence of positive groin nodes, and good results have been reported with hemivulvectomy or radical local excision for the primary tumor** (153). Because these lesions are deep in the vulva, extensive dissection is required in the ischiorectal fossa; even then, surgical margins are often close. Postoperative radiation to the vulva decreased the likelihood of local recurrence from 27% (6 of 22 patients) to 7% (1 of 14 patients) (153). If the ipsilateral groin nodes are positive, bilateral groin and pelvic irradiation may decrease regional recurrence. If the tumor is fixed to the inferior pubic ramus or involves adjacent structures, such as the anal sphincter or rectum, preoperative radiation and chemotherapy is preferable to avoid ultraradical surgery.

Table 36.8 Survival of Patients with Bartholin Gland Carcinoma

<i>FIGO Stage</i>	<i>No. of Patients</i>	<i>No. of Patients with Recurrent Disease</i>	<i>No. of Patients NED at last F/U^a</i>
I	15 (21%)	3 (20%)	14 (93%)
II	16 (23%)	2 (13%)	15 (94%)
III	30 (42%)	11 (37%)	22 (73%)
IV	10 (14%)	5 (50%)	5 (50%)
Total	71 (14%)	21	56 (79%)

FIGO, International Federation of Gynecology and Obstetrics; NED, no evidence of disease; F/U, follow-up.

^aMedian follow-up in each study was at least 5 years.

From references 50, 152, 153, 156

Prognosis

Because of the deep location of the gland, disease tends to be more advanced than squamous carcinomas at the time of diagnosis but, stage for stage, the prognosis is similar. Five-year disease-free survival rates by stage are summarized in Table 36.8.

Adenoid Cystic Carcinoma of the Bartholin Gland

The adenoid cystic variety accounts for 15% of Bartholin gland carcinomas. It is less likely to metastasize to lymph nodes and carries a somewhat better prognosis (50,2) (Fig. 36.8). Local recurrences are common, however, and metastases may occur, particularly to the lungs. The slowly progressive nature of these tumors and the tendency for late

recurrences is reflected in the disparity between progression-free interval and survival curves (157).

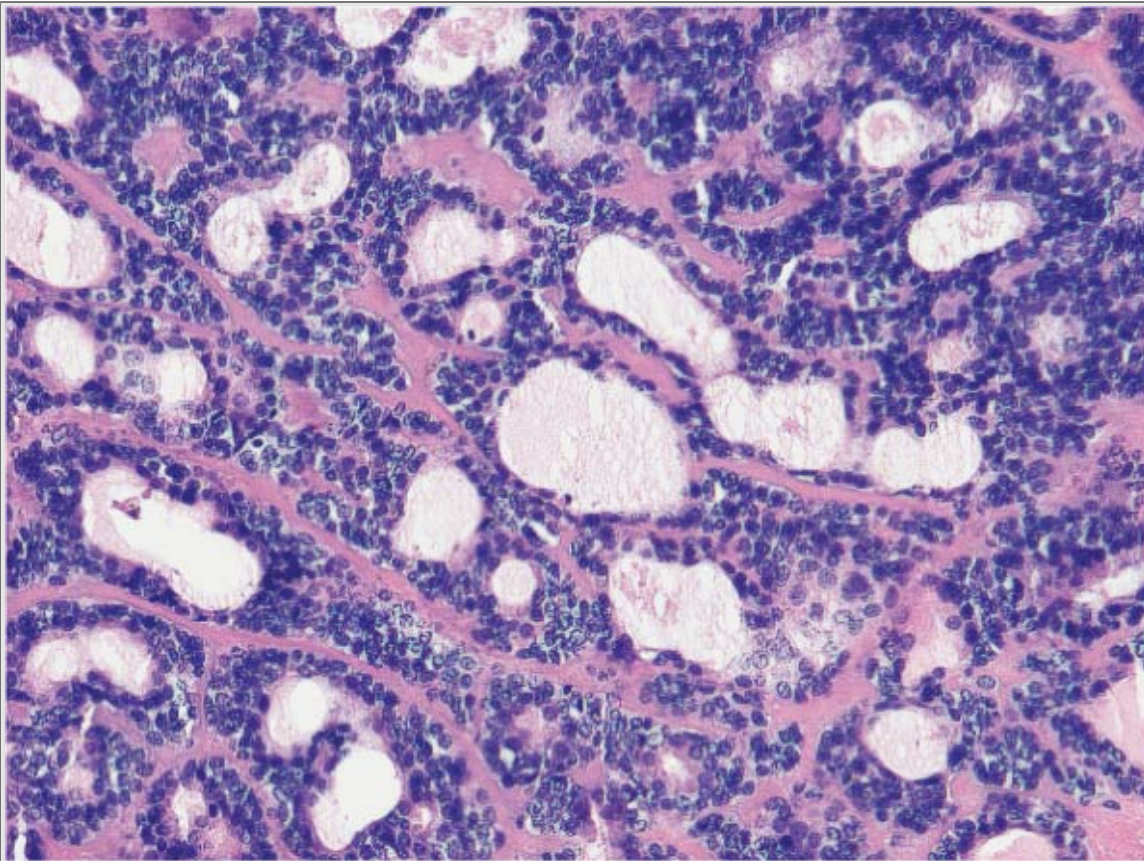


Figure 36.8 Adenoid cystic tumor of the Bartholin gland. Basaloid cells form cribriform, sievelike spaces containing mucinous material. The hyaline stroma is another distinct feature of this tumor.

Other Adenocarcinomas

Adenocarcinomas of the vulva usually arise in a Bartholin gland or occur in association with Paget disease. They may rarely arise from the skin appendages, paraurethral glands, minor vestibular glands, aberrant breast tissue, endometriosis, or a misplaced cloacal remnant (158).

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Adenosquamous Carcinoma

A particularly aggressive type of carcinoma is the adenosquamous carcinoma. This tumor has a number of synonyms, including cylindroma, pseudoglandular squamous cell carcinoma, adenoid squamous cell carcinoma, and adenoacanthoma of the sweat gland of Lever. The tumor has a propensity for perineural invasion, early lymph node metastasis, and local recurrence. One study noted a crude 5-year survival rate of 5.5% (1 of 18) for adenosquamous carcinoma of the vulva, compared with 62.3% (48 of 77) for patients with squamous cell carcinoma (159). Treatment should be radical vulvectomy and bilateral groin dissection. Postoperative radiation therapy may be appropriate.

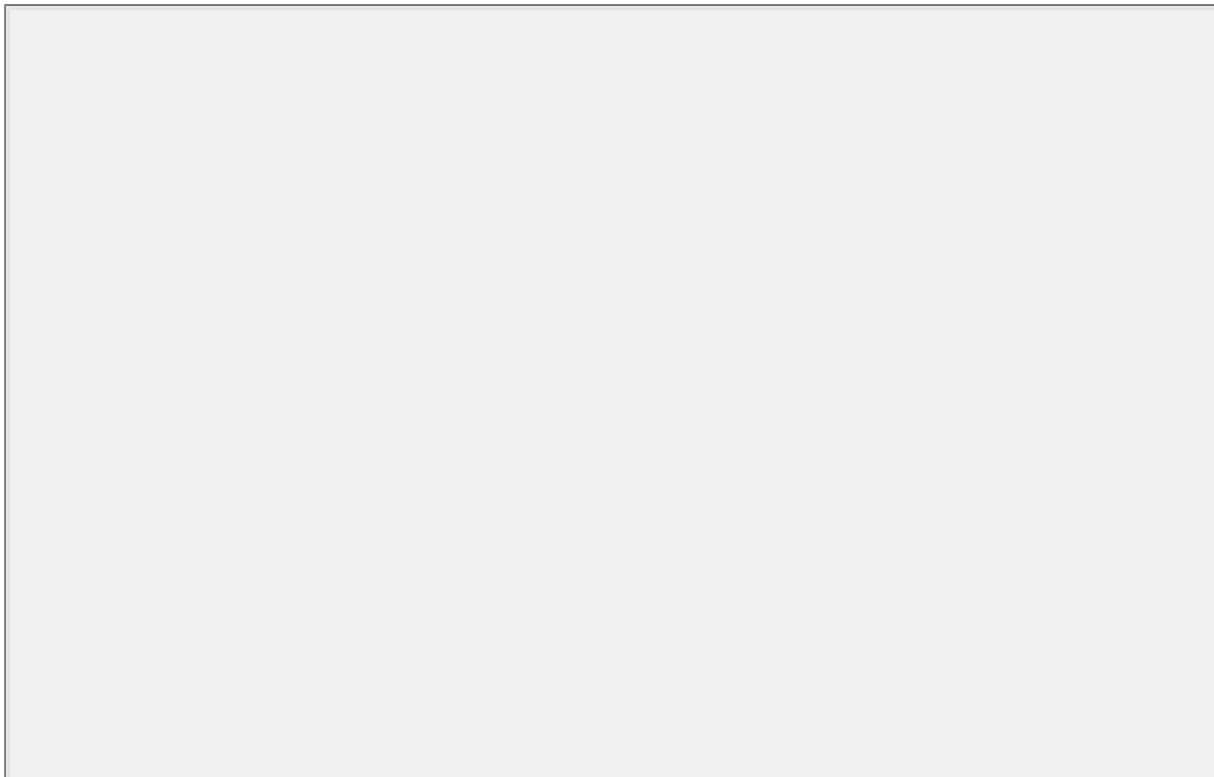
Basal Cell Carcinoma

Basal cell carcinomas represent about 2% of vulvar cancers. As with other basal cell carcinomas, vulvar lesions commonly appear as a "rodent ulcer" with rolled edges, although nodules and macules are other morphologic varieties that occur. Most lesions are smaller than 2 cm in diameter and are usually situated on the anterior labia majora. Giant lesions occasionally occur (160). Basal cell carcinoma usually affects postmenopausal white women and is locally aggressive. Symptoms are frequently present for a prolonged period and most frequently include pruritus, soreness, and irritation (161). It is diagnosed by biopsy, and **radical local excision is generally adequate treatment** (162). **Metastasis to regional lymph nodes has been reported but is rare** (163,164,165). The local recurrence rate is about 10% to 20% (161,2). Basal cell carcinoma of the vulva is associated with a high incidence of antecedent or concomitant malignancies elsewhere (161). In a series of 28 women with vulvar basal cell carcinoma, 10 patients had other basal cell carcinomas, and 10 patients suffered from other primary malignancies (161).

About 3% to 5% of basal cell carcinomas contain a malignant squamous component, the so-called *basosquamous carcinoma*. These lesions are more aggressive and should be treated as squamous carcinomas (165). Another subtype of basal cell carcinoma is the adenoid basal cell carcinoma, which must be differentiated from the more aggressive adenoid cystic carcinoma arising in a Bartholin gland or the skin (165).

Verrucous Carcinoma

Verrucous carcinoma is a variant of squamous cell carcinoma and has distinctive clinical and pathologic characteristics (167). Although most commonly found in the oral cavity, verrucous lesions may be found on any moist membrane composed of squamous epithelium (168). In the female genital tract, these lesions may develop on the cervix, vulva, and vagina. The cause of the lesion in the female genital tract is not fully understood, but associated HPV-6 and HPV-11 have been found in some studies (169), whereas others find it to have no association with HPV infection (170). Some studies have found as many as one third of the cases to have coexisting squamous carcinoma of the vulva (171), underscoring the importance of careful histopathologic assessment of these tumors.



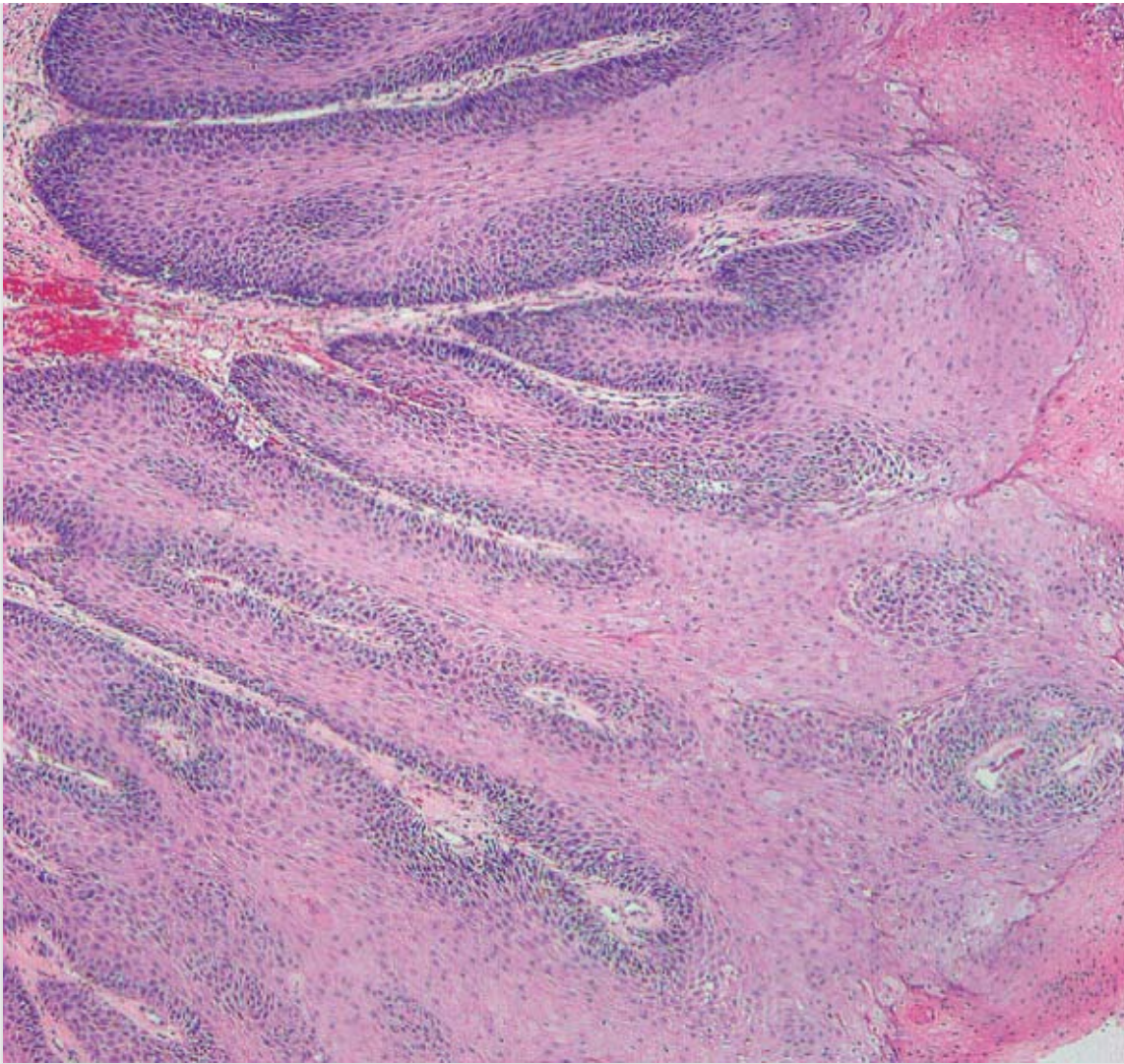


Figure 36.9 Verrucous carcinoma of the vulva. Note the exophytic hyperkeratotic papillary fronds and endophytic bulky rete pegs with smooth borders.

Grossly, the tumors have a cauliflowerlike appearance; microscopically, they contain multiple papillary fronds that lack the central connective tissue core that characterizes condylomata acuminata (Fig. 36.9). The gross and microscopic features of a verrucous carcinoma are very similar to those of the **giant condyloma of Buschke-Loewenstein**, and they probably represent the same disease entity (158). Adequate biopsy from the base of the lesion is required to differentiate a verrucous carcinoma from a benign condyloma acuminatum or a squamous cell carcinoma with a verrucous growth pattern.

Verrucous carcinomas usually occur in postmenopausal women, and they are slow-growing but locally destructive lesions. Even bone may be invaded.

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Metastasis to regional lymph nodes is rare but has been reported (172). Radical local excision is the basic treatment, although any palpably suspicious groin nodes should be evaluated with fine-needle aspiration cytology or excisional biopsy. Usually, enlarged nodes will be caused by inflammatory hypertrophy (173). If the nodes contain metastases, radical vulvectomy and bilateral inguinal-femoral lymphadenectomy are indicated.

Several small studies failed to document any therapeutic advantage with radiation therapy (173,2). In addition, there is concern that radiation may induce anaplastic transformation with subsequent regional and distant metastasis (175). One study reported a corrected 5-

year survival rate of 94% for 17 patients treated with surgery alone, compared with 42% for 7 patients treated with surgery and radiation (173). The latter patients had, however, more advanced disease. If there is a recurrence, further surgical excision is the treatment of choice, which occasionally may necessitate some type of exenteration.

Vulvar Sarcoma

Sarcomas represent 1.5% of vulvar malignancies and constitute a heterogenous group of tumors (176). Leiomyosarcomas are the most common, and other histologic

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types include fibrosarcomas, neurofibrosarcomas, liposarcomas, rhabdomyosarcomas, angiosarcomas, epithelioid sarcomas, and malignant schwannomas.

Leiomyosarcomas usually appear as enlarging, often painful masses, usually in the labium majus. Smooth muscle tumors of the vulva that show at least three of the following four criteria should be regarded as sarcomas: (i) diameter >5 cm, (ii) infiltrating margins, (iii) 5 or more mitotic figures per 10 high-power fields, (iv) moderate-to-severe cytological atypia (177). The absence of one, or even all, of these features does not guarantee against recurrence (178). Lymphatic metastases are uncommon, and radical local excision is the usual treatment.

Epithelioid sarcomas characteristically develop in the soft tissues of the extremities of young adults but rarely may occur on the vulva. In a description of two cases and review of three other reports, the authors concluded that these tumors may mimic a Bartholin cyst, thus leading to inadequate initial treatment (179). They also believed that vulvar epithelioid sarcomas behave more aggressively than their extragenital counterparts, with four of the five patients dying of metastatic disease. They suggested that early recognition and wide excision should improve the prognosis.

Rhabdomyosarcomas are the most common soft tissue sarcomas in childhood, and 20% involve the pelvis or genitourinary tract (180). Dramatic gains have been made in the treatment of these tumors during the past 20 years. Previously, radical pelvic surgery was the standard approach, but results were poor. More recently, a multimodal approach has evolved, and survival rates have improved significantly, with a corresponding decrease in morbidity. In a report of the experience of the Intergroup Rhabdomyosarcoma Study I and II (1972 to 1984) with primary tumors of the female genital tract, nine patients aged 1 to 19 years had primary vulvar tumors, and these tumors were often regarded as a form of Bartholin gland infection before biopsy (181). They were all managed with chemotherapy (*vincristine*, or *actinomycin D* and *cyclophosphamide* and *doxorubicin*), with or without radiotherapy. Wide local excision of the tumor, with or without inguinal-femoral lymphadenectomy, was carried out before or after the chemotherapy. Seven of the nine patients were free of disease 4 or more years from diagnosis, one patient was free of disease when lost to follow-up at 5 years, and one patient was alive with disease.

Rare Vulvar Malignancies

In addition to the previously mentioned tumors, a number of malignancies more commonly seen in other areas of the body may rarely occur as isolated vulvar tumors.

Lymphomas

The genital tract may be involved primarily by malignant lymphomas but, more commonly, involvement is a manifestation of systemic disease. In the lower genital tract, the cervix is most often involved, followed by the vulva and the vagina (182). Most patients are

in their third to sixth decade of life, and about three fourths of the cases involve diffuse large cell or histiocytic non-Hodgkin's lymphomas. The remainder are nodular or Burkitt's lymphomas. Treatment is by surgical excision followed by chemotherapy and radiation or both, and the overall 5-year survival rate is about 70% (182).

Endodermal Sinus Tumor

There have been four case reports of endodermal sinus tumor of the vulva, and three of the four patients died of distant metastases (183). All patients were in their third decade of life, but none was treated with modern chemotherapy.

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Merkel Cell Carcinoma

Merkel cell carcinomas are primary small cell carcinomas of the skin that resemble oat cell carcinomas of the lung. They metastasize widely and have a very poor prognosis (184,2). They should be locally excised and treated with *cisplatin*-based chemotherapy.

Dermatofibrosarcoma Protuberans

This rare, low-grade cutaneous malignancy occasionally involves the vulva. It has a marked tendency for local recurrence but a low risk of systemic spread (186). Radical local excision should be sufficient treatment.

Metastatic Tumors of the Vulva

Eight percent of vulvar tumors are metastatic. The most common primary site is the cervix, followed by the endometrium, kidney, and urethra. Most patients in whom vulvar metastases develop have advanced primary tumors when diagnosed, and in about one fourth of the patients, the primary lesion and the vulvar metastasis are diagnosed simultaneously (187).

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37

Gestational Trophoblastic Disease

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- **Complete molar pregnancies are generally diploid, and all chromosomes are of paternal origin.**
- **Partial molar pregnancies are triploid, and the extra set of chromosomes is paternal.**
- **Complete moles are being diagnosed earlier in pregnancy and less frequently present with the classic signs and symptoms.**
- **Single-agent chemotherapy achieves a high remission rate in nonmetastatic and low-risk metastatic gestational trophoblastic tumors.**
- **After achieving remission with chemotherapy, patients with gestational trophoblastic tumors can generally anticipate normal reproduction in the future.**

Gestational trophoblastic disease (GTD) is among the rare human tumors that can be cured even in the presence of widespread dissemination (1,2). It encompasses

a spectrum of interrelated tumors, including complete and partial hydatidiform mole, placental-site trophoblastic tumor, and choriocarcinoma, which have varying propensities for local invasion and metastasis. Although persistent gestational trophoblastic tumors (GTTs) most commonly follow a molar pregnancy, they can occur after any gestational event, including induced or spontaneous abortion, ectopic pregnancy, or term pregnancy.

Hydatidiform Mole

Epidemiology

Estimates of the incidence of GTD vary dramatically in different regions of the world.

For example, the incidence of molar pregnancy in Japan (2 per 1,000 pregnancies)

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has been reported to be about threefold higher than the incidence in Europe or North America (about 0.6 to 1.1 per 1,000 pregnancies) (3). The variation in the incidence rates of molar pregnancy may in part result from differences between reporting population-based versus hospital-based data. The incidences of both complete and partial mole have been investigated in Ireland by reviewing all products of conception from first- and second-trimester abortions (4). **Based on a thorough pathologic review, the incidence of complete and partial mole was found to be 1 per 1,945 and 1 per 695 pregnancies, respectively.**

Case-control studies have been undertaken to identify risk factors for complete and partial molar pregnancy. The high incidence of molar pregnancy in some populations has been attributed to nutritional and socioeconomic factors. **Case-control studies from Italy and the United States have shown that low dietary intake of carotene may be associated with an increased risk of complete molar pregnancy (5,6). Areas with a high incidence of molar pregnancy also have a high frequency of vitamin A deficiency. Dietary factors, therefore, may partly explain regional variations in the incidence of complete mole.**

Maternal age older than 35 years has consistently been shown to be a risk factor for complete mole. Ova from older women may be more susceptible to abnormal fertilization. In one study, the risk for complete mole was increased 2.0-fold for women older than 35 years and 7.5-fold for women older than 40 years (7).

Limited information is available concerning risk factors for partial molar pregnancy. However, the epidemiologic characteristics of complete and partial mole may differ. The risk for partial mole has been associated with the use of oral contraceptives and a history of irregular menstruation, but not with dietary factors (8). There is no association between maternal age and the risk for partial mole (7).

Complete versus Partial Hydatidiform Mole

Hydatidiform moles may be categorized as either complete or partial moles on the basis of gross morphology, histopathology, and karyotype (Table 37.1).

Complete Hydatidiform Mole

Complete hydatidiform moles exhibit characteristic swelling and trophoblastic

hyperplasia (Fig. 37.1).

They usually have a 46, XX karyotype, although about 10% have a 46, XY karyotype (9). The molar chromosomes are entirely of paternal origin, although mitochondrial DNA is of maternal origin (10,11) (Fig. 37.2). It appears that complete moles usually

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arise from an ovum that has been fertilized by a haploid sperm, which then duplicates its own chromosomes. The ovum nucleus may be either absent or inactivated (12).

<i>Features</i>	<i>Complete Mole</i>	<i>Partial Mole</i>
Fetal or embryonic tissue	Absent	Present
Hydatidiform swelling of chorionic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Karyotype	46, XX (90%); 46, XY	Triploid

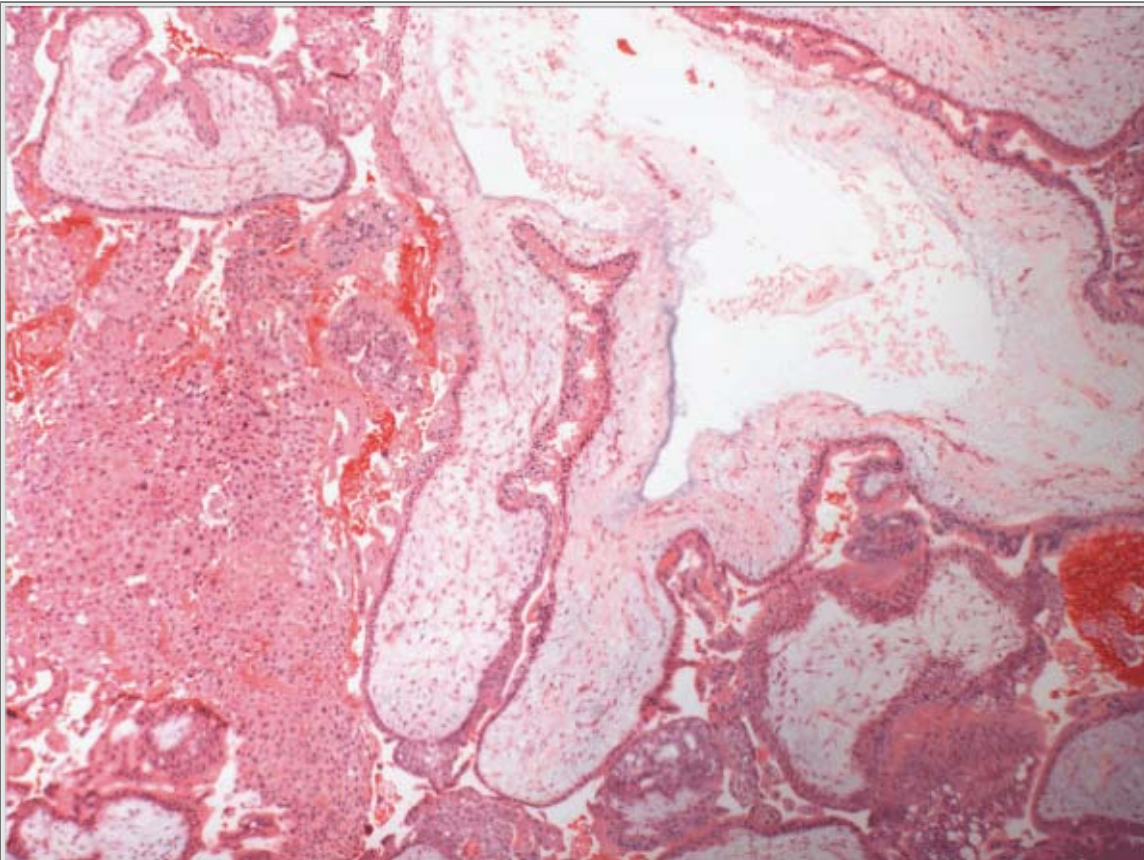


Figure 37.1 Photomicrograph of complete mole demonstrating enlarged villous with central cavitation and surrounding trophoblastic hyperplasia.

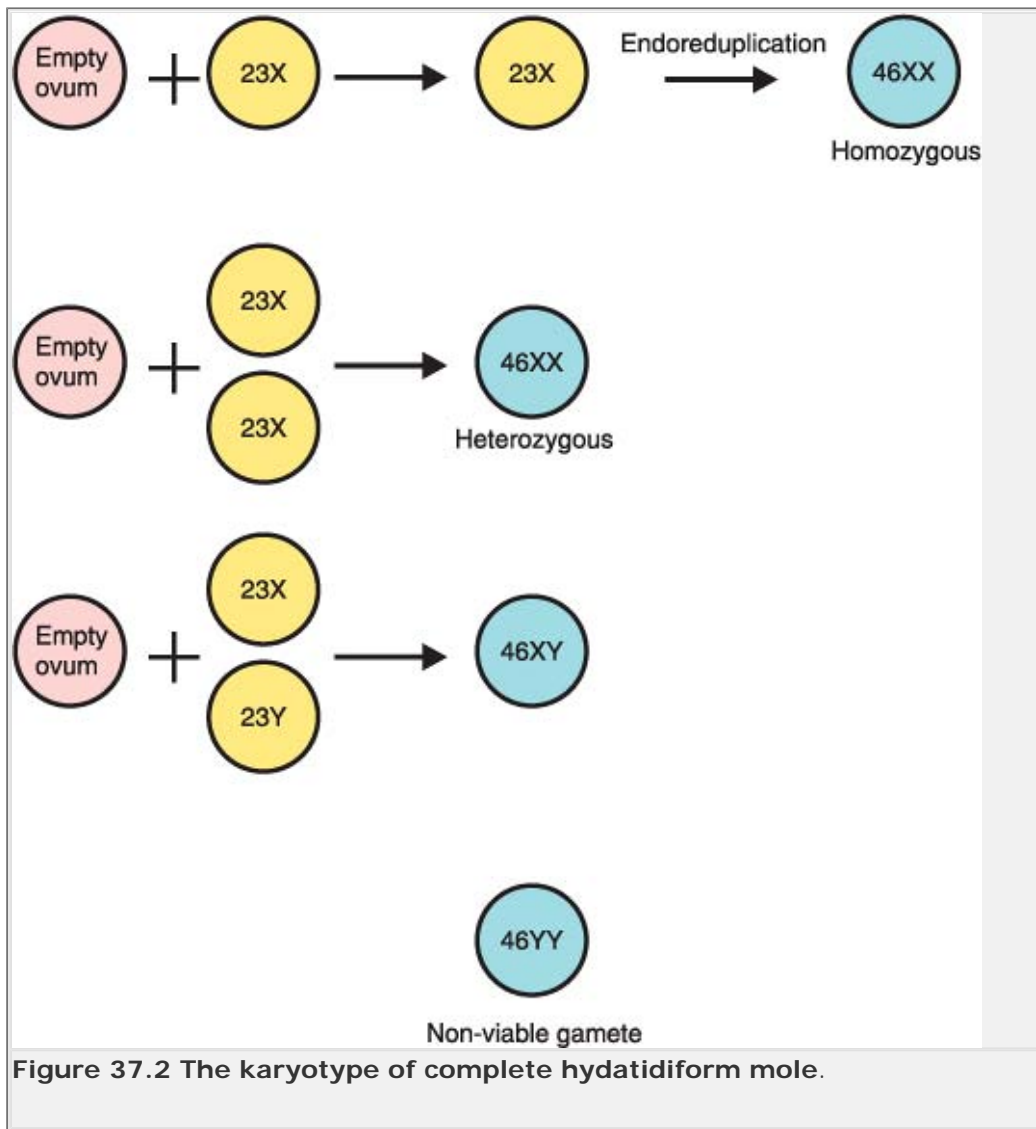


Figure 37.2 The karyotype of complete hydatidiform mole.

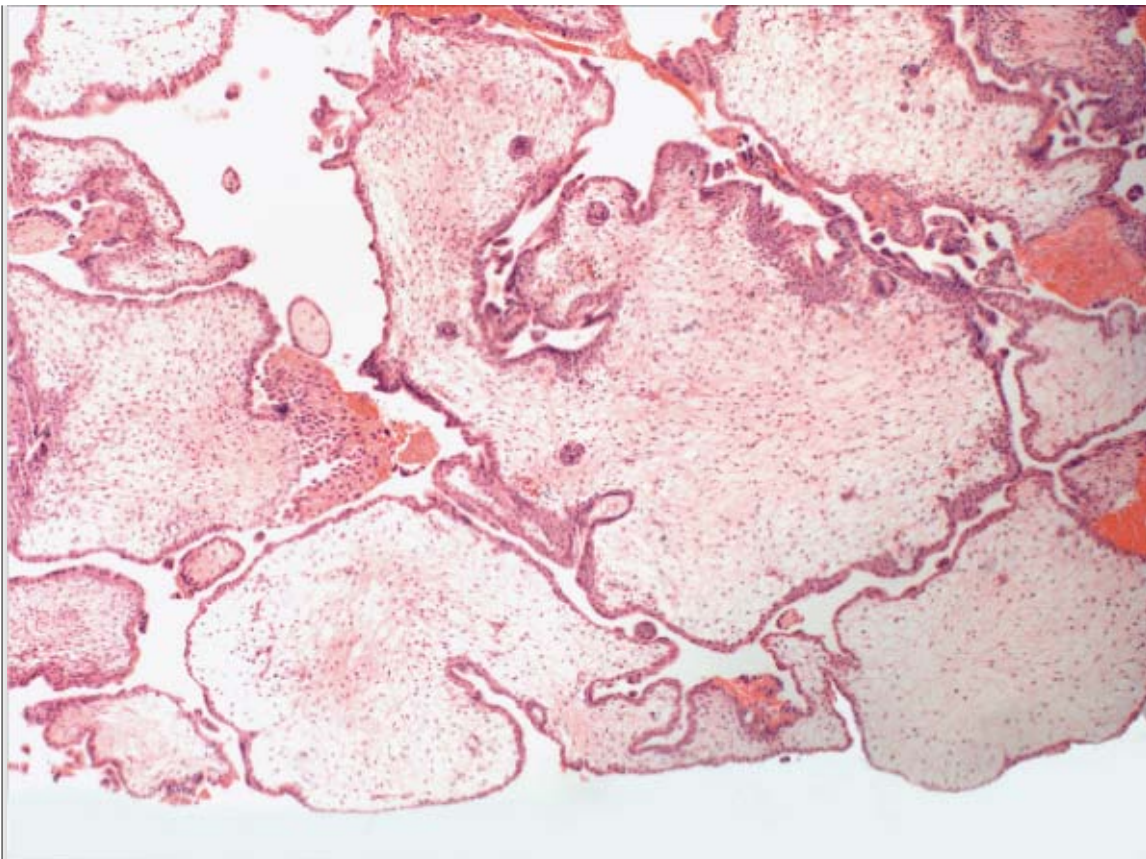


Figure 37.3 Photomicrograph of partial mole showing marked disparity in villous size, trophoblastic inclusions (center), and mild trophoblastic hyperplasia. (From Berkowitz RS, Goldstein OP. Gestational trophoblastic diseases. In: Ryan KJ, Berkowitz R, Barbieri R, eds. *Kistner's gynecology principles and practice*, 5th ed. Chicago, IL: Year Book Medical Publishers, 1990:433, with permission.)

Partial Hydatidiform Mole

Partial hydatidiform moles are characterized by the following pathologic features (13) (Fig. 37.3):

- Chorionic villi of varying size with focal hydatidiform swelling, cavitation, and trophoblastic hyperplasia
- Marked villous scalloping
- Prominent stromal trophoblastic inclusions
- Identifiable embryonic or fetal tissues

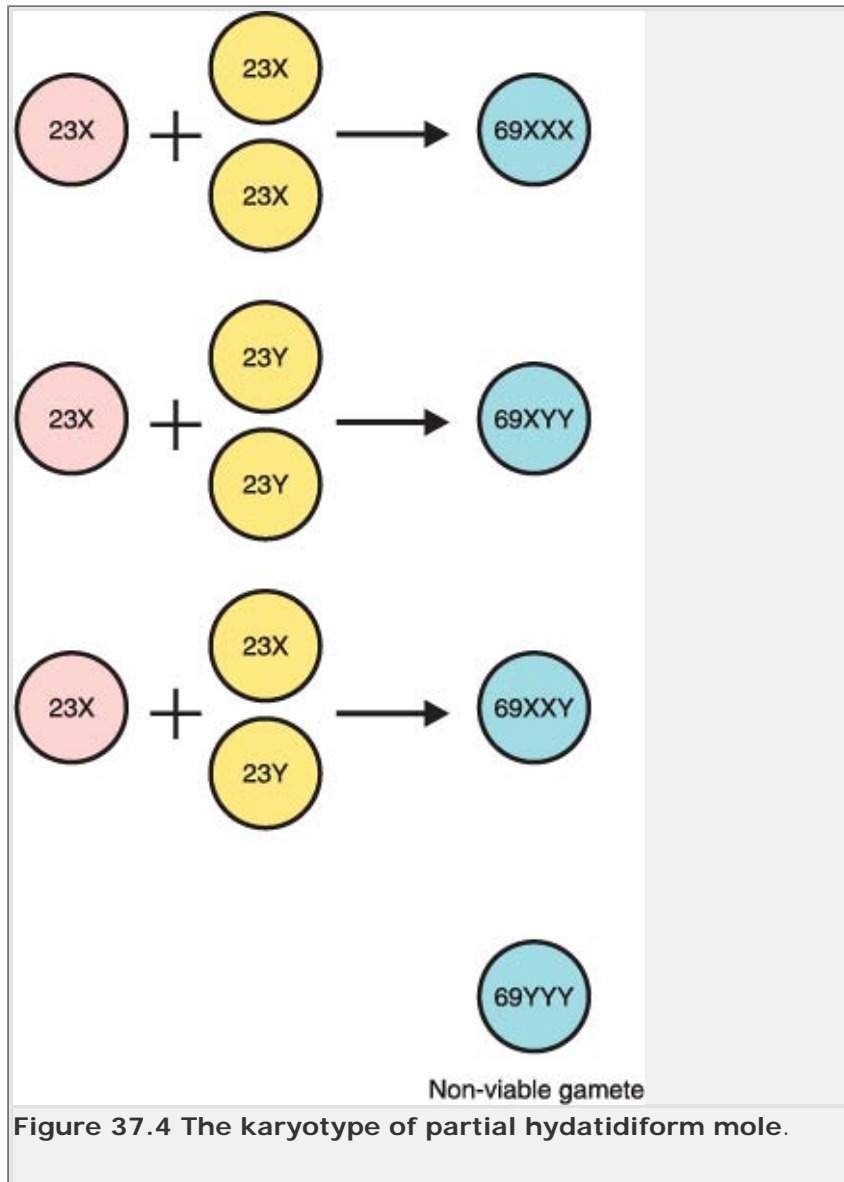
Partial moles generally have a triploid karyotype (69 chromosomes); the extra haploid set of chromosomes usually is derived from the father (Fig. 37.4) (14). It is possible that nontriploid partial moles do not exist (15). When a fetus is present in conjunction with a partial mole, it generally exhibits the stigmata of triploidy, including growth retardation and multiple congenital malformations such as syndactyly and hydrocephaly (Fig. 37.5).

Clinical Features

Patients with complete molar pregnancy are increasingly being diagnosed earlier in pregnancy and treated before they develop the classic clinical signs and symptoms. This may

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be because of changes in clinical practice, such as the frequent use of human chorionic gonadotropin (hCG) measurement and vaginal probe ultrasonography in early pregnancy in women with vaginal staining and even asymptomatic women. Following is a description of the classic and current clinical features of complete molar pregnancy (16).



Complete Hydatidiform Mole

Vaginal Bleeding

Vaginal bleeding is the most common symptom causing patients to seek treatment for complete molar pregnancy. Previously it was reported to occur in 97% of cases, whereas currently it is reported to occur in 84% of patients (17). Molar tissues may separate from the decidua and disrupt maternal vessels, and large volumes of retained blood may distend

the endometrial cavity. Because vaginal bleeding may be considerable and prolonged, one half of these patients had anemia (hemoglobin <10 g/100 mL). Currently anemia is present in only 5% of patients.

Excessive Uterine Size

Excessive uterine enlargement relative to gestational age is one of the classic signs of a complete mole, although it was present in only about one half of patients.

Currently, excessive uterine size occurs in only 28% of patients.

The endometrial cavity may be expanded by both chorionic tissue and retained blood. Excessive uterine size is generally associated with markedly elevated levels of hCG, because uterine enlargement results in part from trophoblastic overgrowth.



Figure 37.5 Photomicrograph of a fetal hand demonstrating syndactyly. The fetus had a triploid karyotype, and the chorionic tissues were a partial mole.

Preeclampsia

Preeclampsia was once observed in 27% of patients with a complete hydatidiform mole. Preeclampsia is now reported in only 1 of 74 patients with complete mole at the initial visit (17). Although preeclampsia is associated with hypertension, proteinuria, and hyperreflexia, eclamptic convulsions rarely occur. Preeclampsia develops almost exclusively in patients with excessive uterine size and markedly elevated hCG levels. Hydatidiform mole should be considered whenever preeclampsia develops early in pregnancy.

Hyperemesis Gravidarum

Hyperemesis requiring antiemetic or intravenous replacement therapy once occurred in one fourth of women with a complete mole, particularly those with excessive uterine size and markedly elevated hCG levels. Severe electrolyte disturbances may develop and require treatment with parenteral fluids. Currently, only 8% of patients have hyperemesis.

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Hyperthyroidism

Clinically evident hyperthyroidism was once observed in 7% of patients with a complete molar gestation. These women may have tachycardia, warm skin, and tremor, and the diagnosis can be confirmed by detection of elevated serum levels of free thyroxine (T_4) and tri-iodothyronine (T_3). Currently, clinical evidence of hyperthyroidism with complete mole is rare.

Anesthesia or surgery may precipitate thyroid storm. Thus, if hyperthyroidism is suspected before the induction of anesthesia for molar evacuation, β -adrenergic blocking agents should be administered. Thyroid storm may be manifested by hyperthermia, delirium, convulsions, tachyarrhythmia, high-output heart failure, or cardiovascular collapse. Administration of β -adrenergic blocking agents prevents or rapidly reverses many of the metabolic and cardiovascular complications of thyroid storm. After molar evacuation, thyroid function test results return rapidly to normal.

Hyperthyroidism develops almost exclusively in patients with very high hCG levels. Some investigators have suggested that hCG is the thyroid stimulator in women with GTD, because positive correlations between serum hCG levels and total T_4 or T_3 concentrations have been observed. However, in one study in which thyroid function was measured in 47 patients with a complete mole, no significant correlation was found between serum hCG levels and serum values of free T_4 index or free T_3 index (18). Although some investigators have speculated about a separate chorionic thyrotropin, this substance has not yet been isolated.

Trophoblastic Embolization

Respiratory distress developed in 2% of patients with a complete mole in the past, but currently rarely occurs. Respiratory distress is usually diagnosed in patients with excessive uterine size and markedly elevated hCG levels. These patients may have chest pain, dyspnea, tachypnea, and tachycardia and may experience severe respiratory distress

during and after molar evacuation. Auscultation of the chest usually reveals diffuse rales, and chest radiographic evaluation may show bilateral pulmonary infiltrates. Respiratory distress usually resolves within 72 hours with cardiopulmonary support. In some circumstances, patients may require mechanical ventilation. Respiratory insufficiency may result from trophoblastic embolization and the cardiopulmonary complications of thyroid storm, preeclampsia, and massive fluid replacement.

Theca Lutein Ovarian Cysts

Prominent theca lutein ovarian cysts (6 cm in diameter) develop in about one half of patients with a complete mole (19). Theca lutein ovarian cysts result from high serum hCG levels, which cause ovarian hyperstimulation (20). Because the uterus also may be excessively enlarged, theca lutein cysts may be difficult to palpate during physical examination; however, ultrasonography can accurately document their presence and size. **After molar evacuation, theca lutein cysts normally regress spontaneously within 2 to 4 months.**

Prominent theca lutein cysts may cause symptoms of marked pelvic pressure, and they can be decompressed by laparoscopic or ultrasonographically directed aspiration. If acute pelvic pain develops, laparoscopy should be performed to assess possible cystic torsion or rupture. Early diagnosis of complete mole not only alters the clinical presentation but also changes the pathologic characteristics. First trimester complete moles have smaller chorionic villi and less extensive trophoblastic hyperplasia and may, therefore, be difficult to distinguish from partial mole or hydropic abortion (21).

Partial Hydatidiform Mole

Patients with partial hydatidiform mole usually do not have the dramatic clinical features characteristic of complete molar pregnancy. **In general, these patients have the signs and symptoms of incomplete or missed abortion, and partial mole can be diagnosed after histologic review of the tissue obtained by curettage (22).**

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In a survey of 81 patients with a partial mole, the main initial sign was vaginal bleeding, which occurred in 59 patients (72.8%) (23). Excessive uterine enlargement and preeclampsia were present in only three patients (3.7%) and two (2.5%) patients, respectively. No patient had theca lutein ovarian cysts, hyperemesis, or hyperthyroidism. The initial clinical diagnosis was an incomplete or missed abortion in 74 patients (91.3%) and hydatidiform mole in only five patients (6.2%). Pre-evacuation hCG levels were measured in 30 patients and were higher than 100,000 mIU/mL in only two patients (6.6%).

Natural History

Complete Hydatidiform Mole

Complete moles have a potential for local invasion and dissemination. **After molar evacuation, local uterine invasion occurs in 15% of patients, and metastasis occurs in 4% (19).**

A review of 858 patients with complete hydatidiform mole revealed that two fifths of the patients had the following signs of marked trophoblastic proliferation at the time they sought treatment (19):

- **hCG level > .100,000 mIU/mL**
- **Excessive uterine enlargement**
- **Theca lutein cysts 6 cm in diameter**

In this review, patients with any one of these signs were considered at high risk for developing postmolar tumor. After molar evacuation, local uterine invasion occurred in 31%, and metastases developed in 8.8% of the 352 high-risk patients. For the 506 low-risk patients, local invasion was found in only 3.4%, and metastases developed in 0.6%.

Older patients are also at increased risk of developing postmolar GTT. One study reported that persistent tumor developed after a complete molar pregnancy in 37% of women older than 40 years (24), whereas in another study this finding occurred in 56% of women older than 50 years (25).

Partial Hydatidiform Mole

Persistent tumor, usually nonmetastatic, develops in approximately 2% to 4% of patients with a partial mole, and chemotherapy is required to achieve remission (26). Patients who develop persistent disease have no distinguishing clinical or pathologic characteristics (27).

Diagnosis

Ultrasonography is a reliable and sensitive technique for the diagnosis of complete molar pregnancy. Because the chorionic villi exhibit diffuse hydropic swelling, complete moles produce a characteristic vesicular ultrasonographic pattern even in the first trimester (Fig 37.6).

Ultrasonography also may contribute to the diagnosis of partial molar pregnancy by demonstrating focal cystic spaces in the placental tissues and an increase in the transverse diameter of the gestational sac (28). When both of these criteria are present, the positive predictive value for partial mole is 90%.

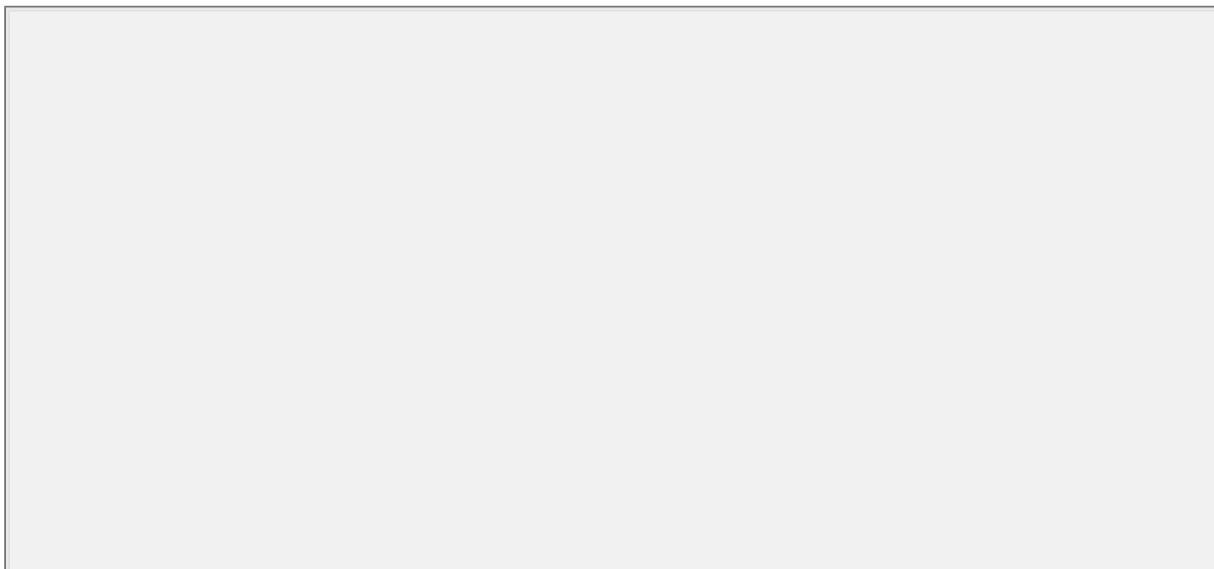




Figure 37.6 Ultrasonogram of a uterus showing a typical pattern of a complete hydatidiform mole. Note the characteristic vesicular ultrasonographic pattern.

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Treatment

After molar pregnancy is diagnosed, the patient should be evaluated carefully for the presence of associated medical complications, including preeclampsia, hyperthyroidism, electrolyte imbalance, and anemia. After the patient's condition has been stabilized, a decision must be made concerning the most appropriate method of evacuation.

Hysterectomy

If the patient desires surgical sterilization, a hysterectomy may be performed with the mole *in situ*. *The ovaries may be preserved at the time of surgery, even in the presence of prominent theca lutein cysts. Large ovarian cysts may be decompressed by aspiration. Hysterectomy does not prevent metastasis; therefore, patients still require follow-up with assessment of hCG levels.*

Suction Curettage

Suction curettage is the preferred method of evacuation, regardless of uterine size, for patients who desire to preserve fertility. It involves the following steps:

- **Oxytocin infusion**—This procedure is begun before the induction of anesthesia.
 - **Cervical dilation**—As the cervix is being dilated, uterine bleeding often increases. Retained blood in the endometrial cavity may be expelled during cervical dilation. However, active uterine bleeding should not deter the prompt completion of cervical dilation.
-
- **Suction curettage**—Within a few minutes of commencing suction curettage, the uterus may decrease dramatically in size, and the bleeding is generally well controlled. The use of a 12-mm cannula is strongly advised to facilitate evacuation. If the uterus is larger than 14 weeks of gestation, one hand should be placed on top of the fundus, and the uterus should be massaged to stimulate uterine contraction and reduce the risk of perforation.
 - **Sharp curettage**—When suction evacuation is believed to be complete, gentle sharp curettage is performed to remove any residual molar tissue.

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Because trophoblast cells express RhD factor, patients who are Rh negative should receive Rh immune globulin at the time of evacuation.

Prophylactic Chemotherapy

The use of prophylactic chemotherapy at the time of molar evacuation is controversial (29). The debate concerns the wisdom of exposing all patients to potentially toxic treatment when only about 20% are at risk of developing persistent tumor.

In a study of 247 patients with complete molar pregnancy who received prophylactically a single course of *actinomycin D* at the time of evacuation, local uterine invasion subsequently developed in only 10 patients (4%), and no patients experienced metastasis (29). Furthermore, all 10 patients with local invasion achieved remission after only one additional course of chemotherapy. **Prophylactic chemotherapy, therefore, not only prevented metastasis but also reduced the incidence and morbidity of local uterine invasion.**

In two prospective randomized studies of prophylactic chemotherapy in patients with a complete mole, a significant decrease in persistent tumor was detected in patients with high-risk mole who received prophylactic chemotherapy (47% and 50% versus 14%) (30,31). **Prophylaxis may be particularly useful in the management of high-risk complete molar pregnancy, especially when hCG assessments for follow-up are unavailable or unreliable.**

Follow-up

Human Chorionic Gonadotropin

After molar evacuation, patients should be monitored with weekly determinations of β -subunit hCG levels until these levels are normal for 3 consecutive weeks, followed

by monthly determinations until the levels are normal for 6 consecutive months. The average time to achieve the first normal hCG level after evacuation is about 9 weeks (32). At the completion of follow-up, pregnancy may be undertaken. After a patient achieves a nondetectable hCG level, the risk of developing tumor relapse is very low and may approach zero (33).

Contraception

Patients are encouraged to use effective contraception during the entire interval of hCG follow-up. Because of the potential risk of uterine perforation, intrauterine devices should not be inserted until the patient achieves a normal hCG level. If the patient does not desire surgical sterilization, either oral contraceptives or barrier methods should be used.

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The incidence of postmolar persistent tumor has been reported to be increased among patients who used oral contraceptives before gonadotropin remission (34). However, more recent data indicate that oral contraceptive use does not increase the risk of postmolar trophoblastic disease (35,36). **It appears that oral contraceptives may be used safely after molar evacuation during the entire interval of hormonal follow-up.**

Persistent Gestational Trophoblastic Tumor

Nonmetastatic Disease

Locally invasive GTT develops in about 15% of patients after evacuation of a complete mole and infrequently after other gestations (1). These patients usually present with the following symptoms:

- Irregular vaginal bleeding
- Theca lutein cysts
- Uterine subinvolution or asymmetric enlargement
- Persistently elevated serum hCG levels.

The trophoblastic tumor may perforate the myometrium, causing intraperitoneal bleeding, or erode into uterine vessels, causing vaginal hemorrhage. Bulky, necrotic tumor may involve the uterine wall and serve as a nidus for infection. Patients with uterine sepsis may have a purulent vaginal discharge and acute pelvic pain.

After molar evacuation, persistent GTT may exhibit the histologic features of either hydatidiform mole or choriocarcinoma. After a nonmolar pregnancy, however, persistent GTT always has the histologic pattern of choriocarcinoma. Histologically, choriocarcinoma is characterized by sheets of anaplastic syncytiotrophoblast and cytotrophoblast without chorionic villi.

Placental-site Trophoblastic Tumor

Placental-site trophoblastic tumor is an uncommon but important variant of choriocarcinoma that consists predominantly of intermediate trophoblast (37). Relative to their mass, these tumors produce small amounts of hCG and human placental lactogen (hPL), and they tend to remain confined to the uterus, metastasizing late in their course. In contrast to other trophoblastic tumors, placental-site tumors are relatively insensitive to chemotherapy.

Metastatic Disease

Metastatic GTT occurs in about 4% of patients after evacuation of a complete mole, but it is seen more often when GTT develops after nonmolar pregnancies (1). Metastasis is usually associated with choriocarcinoma, which has a tendency toward early vascular invasion with widespread dissemination. Because trophoblastic tumors often are perfused by fragile vessels, they are frequently hemorrhagic. Symptoms of metastases may result from spontaneous bleeding at metastatic foci. The most common sites of metastases are lung (80%), vagina (30%), pelvis (20%), liver (10%), and brain (10%).

Pulmonary

At the time of diagnosis, lung involvement is visible by chest radiography in 80% of patients with metastatic GTT. Patients with pulmonary metastasis may have chest pain, cough, hemoptysis, dyspnea, or an asymptomatic lesion visible by chest radiography. Respiratory symptoms may be acute or chronic, persisting over many months.

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GTT may produce four principal pulmonary patterns:

- An alveolar or "snowstorm" pattern
- Discrete rounded densities
- Pleural effusion
- An embolic pattern caused by pulmonary arterial occlusion

Because respiratory symptoms and radiographic findings may be dramatic, the patient may be thought to have a primary pulmonary disease. Some patients with extensive pulmonary involvement have minimal, if any, gynecologic symptoms because the reproductive organs may be free of trophoblastic tumor. Unfortunately, the diagnosis of GTT may be confirmed only after thoracotomy has been performed, particularly in patients with a nonmolar antecedent pregnancy.

Pulmonary hypertension may develop in patients with GTT secondary to pulmonary arterial occlusion by trophoblastic emboli. The development of early respiratory failure requiring intubation is associated with a poor clinical outcome (38).

Vaginal

Vaginal metastases occurs in 30% of the patients with metastatic tumor. These lesions are usually highly vascular and may bleed vigorously when biopsied. Metastases

to the vagina may occur in the fornices or suburethrally and may produce irregular bleeding or a purulent discharge.

Hepatic

Liver metastases occur in 10% of patients with disseminated trophoblastic tumor.

Hepatic involvement is encountered almost exclusively when there is a protracted delay in diagnosis and the patient has an extensive tumor burden. Epigastric or right upper quadrant pain may develop if metastases stretch the hepatic capsule. Hepatic lesions may be hemorrhagic, causing hepatic rupture and exsanguinating intraperitoneal bleeding.

Central Nervous System

Metastatic trophoblastic disease involves the brain in 10% of patients. Cerebral involvement is generally seen in patients with advanced disease; virtually all patients with brain metastasis have concurrent pulmonary or vaginal involvement or both. Because cerebral lesions may hemorrhage spontaneously, patients may develop acute focal neurologic deficits.

Staging

An anatomic staging system for GTT has been adopted by the International Federation of Gynecology and Obstetrics (FIGO) (Table 37.2). It is hoped that this staging system will encourage the objective comparison of data from various centers (39).

Stage I: Patients have persistently elevated hCG levels and tumor confined to the uterine corpus.

Stage II: Patients have metastases to the vagina and pelvis or both.

Stage III: Patients have pulmonary metastases with or without uterine, vaginal, or pelvic involvement. The diagnosis is based on a rising hCG level in the presence of pulmonary lesions viewed by chest radiography.

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Stage IV: Patients have advanced disease and involvement of the brain, liver, kidneys, or gastrointestinal tract. These patients are in the highest risk category because they are most likely to be resistant to chemotherapy. Choriocarcinoma is usually present, and the disease commonly follows a nonmolar pregnancy.

Table 37.2 Staging of Gestational Trophoblastic Tumors^{a,b}

Stage I	Disease confined to uterus
Ia	Disease confined to uterus with no risk factors
Ib	Disease confined to uterus with one risk factor
Ic	Disease confined to uterus with two risk factors
Stage II	Gestational trophoblastic tumor extending outside uterus but limited to genital structures (adnexa, vagina, broad ligament)
IIa	Gestational trophoblastic tumor involving genital structures without risk factors
IIb	Gestational trophoblastic tumor extending outside uterus but limited to genital structures with one risk factor
IIc	Gestational trophoblastic tumor extending outside uterus but limited to genital structures with two risk factors

Stage III	<i>Gestational trophoblastic disease extending to lungs with or without known genital tract involvement</i>
IIIa	Gestational trophoblastic tumor extending to lungs with or without genital tract involvement and with no risk factors
IIIb	Gestational trophoblastic tumor extending to lungs with or without genital tract involvement and with one risk factor
IIIc	Gestational trophoblastic tumor extending to lungs with or without genital tract involvement and with two risk factors
Stage IV	<i>All other metastatic sites</i>
IVa	All other metastatic sites without risk factors
IVb	All other metastatic sites with one risk factor
IVc	All other metastatic sites with two risk factors

^aRisk factors affecting staging include the following: (i) human chorionic gonadotropin > .100,000 mIU/mL and (ii) duration of disease longer than 6 months from termination of antecedent pregnancy.

^bThe following factors should be considered and noted in reporting: (i) prior chemotherapy has been given for known gestational trophoblastic tumor, (ii) placental site tumors should be reported separately, and (iii) histologic verification of disease is not required.

Prognostic Scoring

In addition to anatomic staging, it is important to consider other variables to predict the likelihood of drug resistance and to assist in selecting appropriate chemotherapy (40). **A prognostic scoring system proposed by the World Health Organization reliably predicts the potential for resistance to chemotherapy** (Table 37.3).

	0	1	2	4
Age (years)	≤ 39	> 39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Interval between end of antecedent pregnancy and start of chemotherapy (months)	<4	4–6	7–12	>12
Human chorionic gonadotropin (IU/L)	<10 ³	10 ³ –10 ⁴	10 ⁴ –10 ⁵	>10 ⁵
ABO groups		O or A	B or AB	
Largest tumor, including uterine (cm)	<3	3–5	>5	
Site of metastases		Spleen kidney	Gastrointestinal tract, liver	Brain
Number of metastases		1–3	4–8	8
Prior chemotherapy			1 drug	2 drugs

^aThe total score for a patient is obtained by adding the individual scores for each prognostic factor. Total score: <4, low risk; 5–7, middle risk; ≥8, high risk.

When the prognostic score is higher than 7, the patient is categorized as high risk and requires intensive combination chemotherapy to achieve remission. Patients with stage I disease usually have a low-risk score, and those with stage IV disease have a high-risk score. The distinction between low and high risk applies mainly to patients with stage II or III disease.

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Diagnostic Evaluation

Optimal management of persistent GTT requires a thorough assessment of the extent of the disease before the initiation of treatment. **All patients with persistent GTT should undergo a careful pretreatment evaluation, including the following:**

- Complete history and physical examination
- Measurement of the serum hCG value
- Hepatic, thyroid, and renal function tests
- Determination of baseline peripheral white blood cell and platelet counts

The metastatic workup should include the following:

- Chest radiograph or computed tomography (CT) scan
- Ultrasonography or CT scan of the abdomen and pelvis
- CT or magnetic resonance imaging (MRI) scan of the head

When the pelvic examination and chest radiographic findings are negative, metastatic involvement of other sites is uncommon.

Liver ultrasonography and CT or MRI scanning will disclose most hepatic metastases in patients with abnormal liver function tests. CT or MRI scan of the head has facilitated the early diagnosis of asymptomatic cerebral lesions. Chest CT scans may detect micrometastases not visible on chest radiography. Chest CT will demonstrate pulmonary micrometastases in about 40% of patients with presumed nonmetastatic disease (41).

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In patients with choriocarcinoma or metastatic disease, hCG levels may be measured in the cerebrospinal fluid (CSF) to exclude cerebral involvement if the results of CT scanning of the brain are normal. The ratio of plasma-to-CSF hCG tends to be lower than 60 in the presence of cerebral metastases (42). However, a single plasma-to-CSF hCG ratio may be misleading, because rapid changes in plasma hCG levels may not be reflected promptly in the CSF (43).

Pelvic ultrasonography appears to be useful in detecting extensive trophoblastic uterine involvement and may also aid in identifying sites of resistant uterine tumor

(44). Because ultrasonography can accurately and noninvasively detect extensive uterine tumor, it may help identify patients who would benefit from hysterectomy.

Table 37.4 Protocol for Treatment of Gestational Trophoblastic Tumor

Stage I	
Initial	Single-agent chemotherapy or hysterectomy with adjunctive chemotherapy
Resistant	Combination chemotherapy
	Hysterectomy with adjunctive chemotherapy
	Local resection
	Pelvic infusion
Stage II and III	
Low risk^a	
Initial	Single-agent chemotherapy
Resistant	Combination chemotherapy
High risk^a	
Initial	Combination chemotherapy
Resistant	Second-line combination chemotherapy
Stage IV	
Initial	Combination chemotherapy
Brain	Whole-head irradiation (3,000 cGy)
	Craniotomy to manage complications
Liver	Resection to manage complications
Resistant^a	Second-line combination chemotherapy
	Hepatic arterial infusion

^aLocal resection optional.

Management of Persistent GTT

A protocol for the management of GTT is presented in Table 37.4.

Stage I

In patients with stage I disease, the selection of treatment is based primarily on whether the patient desires to retain fertility.

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Hysterectomy plus Chemotherapy

If the patient does not wish to preserve fertility, hysterectomy with adjuvant single-agent chemotherapy may be performed as primary treatment. Adjuvant chemotherapy is administered for three reasons:

- To reduce the likelihood of disseminating viable tumor cells at surgery

To maintain a cytotoxic level of chemotherapy in the bloodstream and tissues in case viable tumor cells are disseminated at surgery

To treat any occult metastases that may already be present at the time of surgery

Chemotherapy can be administered safely at the time of hysterectomy without increasing the risk of bleeding or sepsis. In a series of 31 patients treated with primary hysterectomy and a single course of adjuvant chemotherapy, all achieved complete remission with no additional therapy.

Hysterectomy also is performed in all patients with stage I placental-site trophoblastic tumor. Because placental-site tumors are resistant to chemotherapy, hysterectomy for presumed nonmetastatic disease is the only curative treatment. Patients with metastatic placental site trophoblastic tumor may still achieve remission but their tumors are less responsive to chemotherapy (45).

Chemotherapy Alone

Single-agent chemotherapy is the preferred treatment in patients with stage I disease who desire to retain fertility. When primary single-agent chemotherapy was administered to 495 patients with stage I GTT, 452 patients (91.3%) attained complete remission. The remaining 43 resistant patients subsequently achieved remission after combination chemotherapy or surgical intervention.

When patients are resistant to single-agent chemotherapy and desire to preserve fertility, combination chemotherapy should be administered. If the patient is resistant to both single-agent and combination chemotherapy and wants to retain fertility, local uterine resection may be considered. When local resection is planned, a preoperative ultrasonography, MRI, or arteriography may help to define the site of the resistant tumor.

Stages II and III

Vaginal and Pelvic Metastasis

Low-risk patients treated with primary single-agent chemotherapy have a high (approximately 80%) rate of remission. High-risk patients often do not achieve remission with single-agent treatment and are treated with primary intensive combination chemotherapy.

Vaginal metastases may bleed profusely because they are highly vascular and friable. When bleeding is substantial, it may be controlled by packing the vagina or by wide local excision. Infrequently, arteriographic embolization of the hypogastric arteries may be required to control hemorrhage from vaginal metastases.

Pulmonary Metastasis

Of 153 patients treated with stage III disease, 152 (99%) attained complete remission. Gonadotropin remission was induced with single-agent chemotherapy in 85 of 104

(81.7%) patients with low-risk disease. All patients who were resistant to single-agent treatment subsequently achieved remission with combination chemotherapy.

Thoracotomy

Thoracotomy has a limited role in the management of stage III disease. **If a patient has persistent viable pulmonary metastasis following intensive chemotherapy, however, thoracotomy may be attempted to excise the resistant focus.** A thorough metastatic workup should be performed before surgery to exclude other sites of persistent disease. Fibrotic pulmonary nodules may persist indefinitely on chest radiography, even after complete gonadotropin remission has been attained. In patients undergoing thoracotomy for resistant disease, chemotherapy should be administered postoperatively to treat potential occult sites of micrometastasis.

Hysterectomy

Hysterectomy may be required in patients with metastatic disease to control uterine hemorrhage or sepsis. Furthermore, in patients with extensive uterine tumor, hysterectomy may substantially reduce the trophoblastic tumor burden and thereby limit the need for multiple courses of chemotherapy.

Follow-up

All patients with stage I through stage III disease should receive follow-up with:

- **Weekly measurement of hCG levels until they are normal for 3 consecutive weeks**
- **Monthly measurement of hCG values until levels are normal for 12 consecutive months**
- **Effective contraception during the entire interval of hormonal follow-up**

Stage IV

All patients with stage IV disease should be treated with primary intensive combination chemotherapy and the selective use of radiation therapy and surgery.

Before 1975, only 6 of 20 patients (30%) treated with stage IV disease attained complete remission, whereas after that time, 15 of 19 patients (78.9%) achieved remission. This improvement in survival has resulted from the use of primary combination chemotherapy in conjunction with radiation and surgical treatment. Patients with stage IV disease are at greatest risk of developing rapidly progressive and unresponsive tumors despite intensive multimodal therapy. They should preferably be referred to centers with special expertise in the management of trophoblastic disease.

Hepatic Metastasis

The management of hepatic metastasis is particularly difficult. If a patient is resistant to systemic chemotherapy, hepatic arterial infusion of chemotherapy may induce complete remission in selected cases. Hepatic resection may also be required to control acute bleeding or to excise a focus of resistant tumor. New techniques of arterial embolization may reduce the need for surgical intervention.

Cerebral Metastasis

If cerebral metastases are diagnosed, whole-brain irradiation (3,000 cGy in 10 fractions) can be instituted promptly. Because irradiation may be both hemostatic and tumoricidal, the risk of spontaneous cerebral hemorrhage may be lessened by the concurrent use of combination chemotherapy and brain irradiation. However, excellent remission rates

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(86%) have been reported in patients with cranial metastases treated with intensive intravenous combination chemotherapy and intrathecal *methotrexate* (MTX) (46).

Craniotomy

Craniotomy may be required to provide acute decompression or to control bleeding.

It should be performed to manage life-threatening complications in the hope that the patient ultimately will be cured with chemotherapy. In one study (47), the use of craniotomy to control bleeding in six patients resulted in complete remission in three patients.

Infrequently, cerebral metastases that are resistant to chemotherapy may be amenable to local resection. Fortunately, patients with cerebral metastases who achieve sustained remission generally have no residual neurologic deficits.

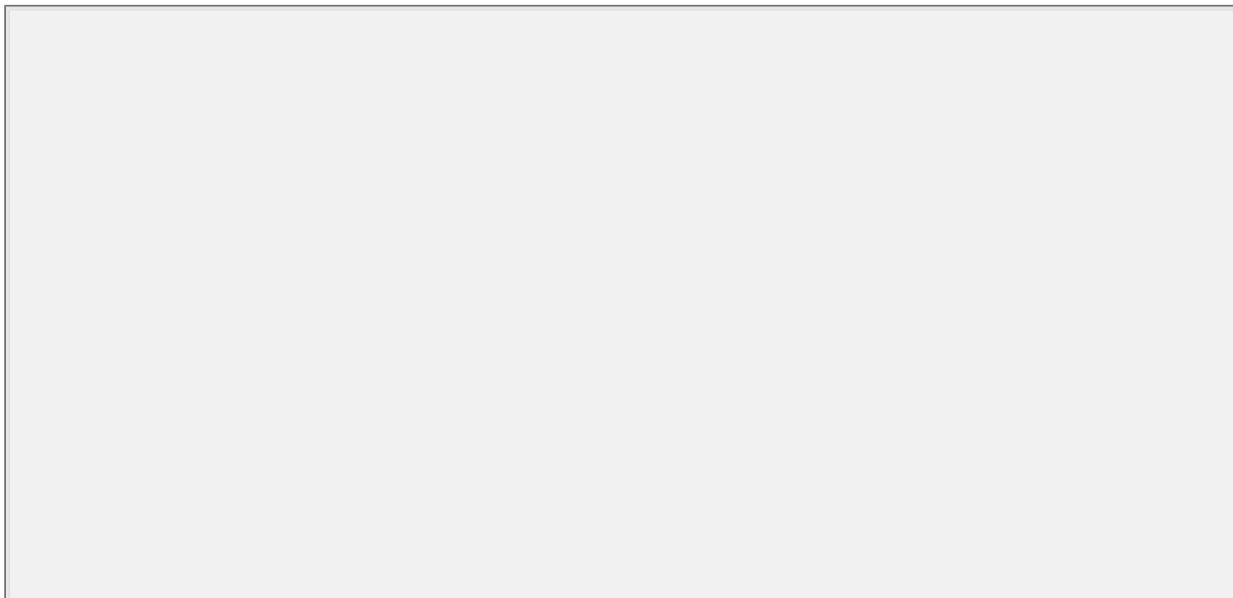
Follow-up

Patients with stage IV disease should receive follow-up with:

- Weekly determination of hCG levels until they are normal for 3 consecutive weeks
- Monthly determination of hCG levels until they are normal for 24 consecutive months

These patients require prolonged gonadotropin follow-up because they are at increased risk of late recurrence.

An algorithm for the management of persistent GTT is presented in Figure 37.7.



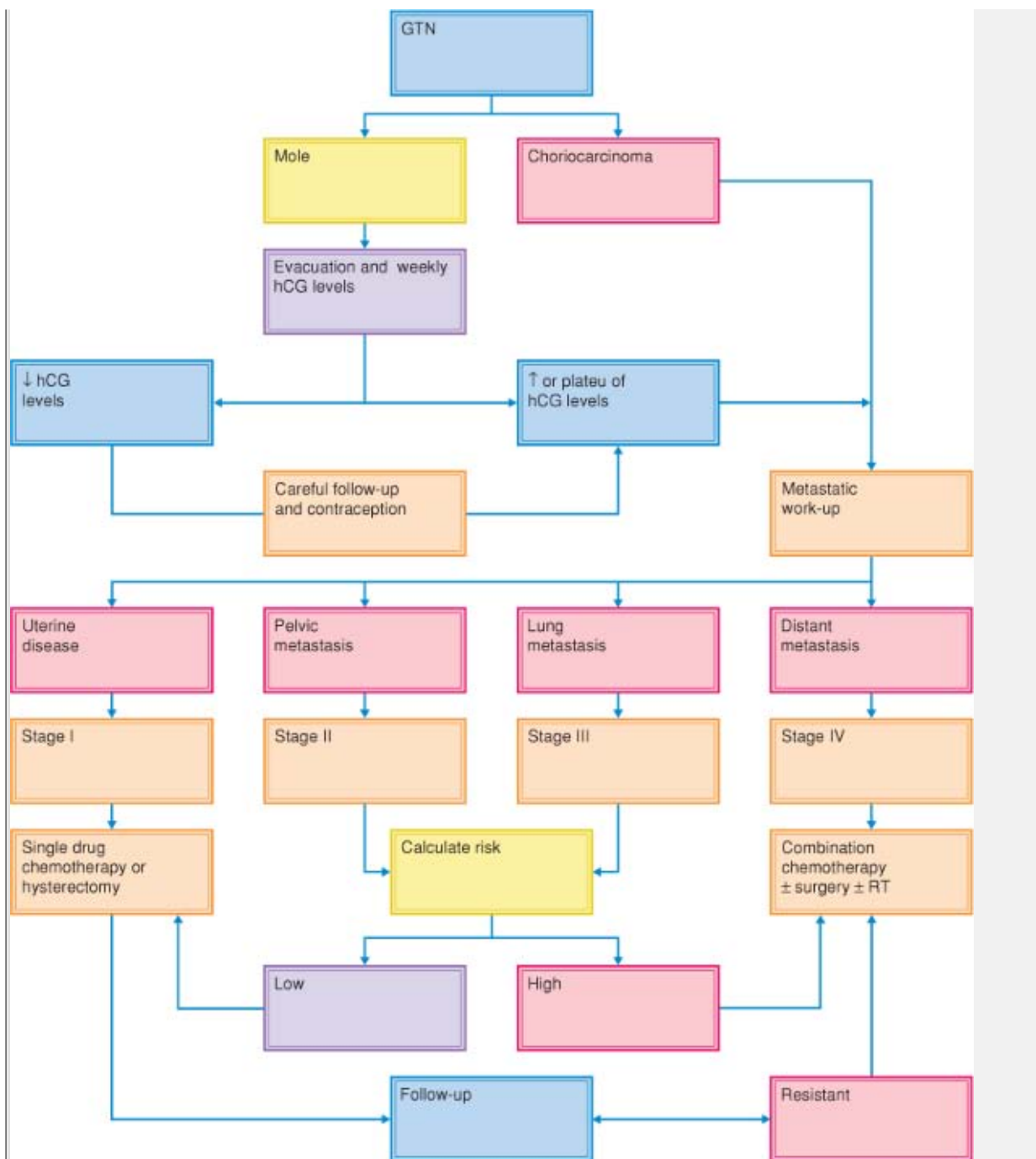


Figure 37.7 Algorithm for the management of persistent gestational trophoblastic tumor. GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; RT, radiotherapy. (From **Berkowitz RS, Goldstein DP.** Gestational trophoblastic neoplasia. In: **Berek JS, Hacker NF,** eds. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005;618, with permission.)

Chemotherapy

Single-Agent Treatment

Single-agent chemotherapy with either actinomycin D (Act-D) or MTX has achieved comparable and excellent remission rates in both nonmetastatic and low-risk metastatic GTT (48). Several protocols using these agents are available. *Act-D* can be given every other week as a 5-day regimen or in a pulsatile fashion; similarly, *MTX* can be given either in a 5-day regimen

or pulsatile weekly. No study has compared all of these protocols with regard to success. An optimal regimen should maximize the response rate while minimizing morbidity and cost.

The administration of *methotrexate* with *folinic acid* (*MTX-FA*) in GTT to limit systemic toxicity was first reported in 1964 (49). Subsequently, it has been confirmed that *MTX-FA* is both effective and safe in the management of GTT (50).

An evaluation of 185 patients treated with *MTX-FA* revealed that complete remission was achieved in 162 patients (87.6%); of these patients, 132 (81.5%) required only one course of *MTX-FA* to attain remission (50). *MTX-FA* induced remission in 147 of 163 patients (90.2%) with stage I GTT and in 15 of 22 patients (68.2%) with low-risk stages II and III GTT. Resistance to therapy was more common in patients with choriocarcinoma, metastasis, and pretreatment serum hCG levels higher than 50,000 mIU/mL. After treatment with *MTX-FA*, thrombocytopenia, granulocytopenia, and hepatotoxicity developed in only 3 (1.6%), 11 (5.9%), and 26 (14.1%) patients, respectively. **Thus**, *MTX-FA* achieved an excellent therapeutic outcome with minimal toxicity and attained this goal with limited exposure to chemotherapy.

Technique of Single-agent Treatment

The serum hCG level is measured weekly after each course of chemotherapy.

The Treatment hCG regression curve serves as the primary basis for determining the need for additional treatment.

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After the first treatment:

- **Further chemotherapy is withheld as long as the hCG level is falling progressively.**
- **Additional single-agent chemotherapy is not administered at any predetermined or fixed interval.**

A second course of chemotherapy is administered under the following conditions:

- **If the hCG level plateaus for more than 3 consecutive weeks or begins to rise again**
- **If the hCG level does not decline by 1 log within 18 days after completion of the first treatment**

If the patient's response to the first treatment was adequate and a second course of *MTX-FA* is required, the dosage of *MTX* is unaltered. An adequate response is defined as a fall in the hCG level by 1 log after a course of chemotherapy.

If the response to the first treatment is inadequate, the dosage of *MTX* is increased from 1.0 mg/kg per day to 1.5 mg/kg per day for each of the 4 treatment days. If the response to two consecutive courses of *MTX-FA* is inadequate, the patient is considered to be resistant to *MTX*, and *Act-D* is promptly substituted. If the hCG levels do not decline by 1

log after treatment with *Act-D*, the patient also is considered resistant to *Act-D* as a single agent. She must then be treated intensively with combination chemotherapy to achieve remission.

Combination Chemotherapy

Triple Therapy

Triple therapy with *MTX*, *Act-D*, and *cyclophosphamide* is inadequate as an initial treatment in patients with metastasis and a high-risk prognostic score.

Collectively, data from three centers indicate that triple therapy induced remission in only 21 (49%) of 43 patients with metastasis and a high-risk score (score >7) (51,52,53).

EMA-CO

Etoposide has been reported to induce complete remission in 56 (95%) of 60 patients with nonmetastatic and low-risk metastatic GTT (54). A new combination regimen described in 1984 included *etoposide*, *MTX*, *Act-D*, *cyclophosphamide*, and *vincristine* (*EMA-CO*) and had an 83% remission in patients with metastasis and a high-risk score (55). Another study confirmed that primary *EMA-CO* induced complete remission in 76% of the patients with metastatic GTT and a high-risk score (56). Still another study reported that *EMA-CO* induced complete sustained remission in 87 (90.6%) of 96 patients with high-risk (score >7) GTT (57). Furthermore, remission occurred with *EMA-CO* in 30 (86%) of 35 patients with brain metastasis (46).

The *EMA-CO* regimen is generally well tolerated, and treatment seldom has to be suspended because of toxicity. The *EMA-CO* regimen is the preferred primary treatment in patients with metastasis and a high-risk prognostic score. However, the optimal combination drug protocol for management of GTT has not yet been clearly defined. If patients experience resistance to

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EMA-CO, they may then be treated successfully by substituting *etoposide* and *cisplatin* on day 8 (*EMA-EP*). *EMA-EP* has induced remission alone or with surgery in 16 (76%) of 21 patients who were resistant to *EMA-CO* (58). The optimal combination drug protocol will most likely include *etoposide*, *MTX*, and *Act-D* and perhaps other agents administered in the most dose-intensive manner.

Duration of Therapy

Patients who require combination chemotherapy must be treated intensively to attain remission. Combination chemotherapy should be given as often as toxicity permits until the patient achieves three consecutive normal hCG levels. After normal hCG levels are attained, at least two additional courses of chemotherapy are administered to reduce the risk of relapse.

Subsequent Pregnancies

Pregnancies after Hydatidiform Mole

Patients with hydatidiform moles can anticipate normal reproduction in the future (59). From 1965 until 2001, patients who were treated for complete mole had 1,278 subsequent pregnancies that resulted in 877 term live births (68.6%), 95 premature deliveries (7.4%), 11 ectopic pregnancies (0.9%), 7 stillbirths (0.5%), and 18 repeat

molar pregnancies (1.4%). First- and second-trimester spontaneous abortions occurred in 229 (17.9%) pregnancies. Major and minor congenital malformations were detected in 40 infants (4.1%), and primary cesarean delivery was performed in 70 of 373 (18.8%) term or preterm births from 1979 to 2001.

Although data regarding pregnancies after partial mole are limited (251 subsequent pregnancies), the information is reassuring (59). **Patients with both complete and partial mole should be reassured that they are at no increased risk of complications in later gestations.**

When a patient has had a molar pregnancy, she is at an increased risk of having a molar gestation in subsequent conceptions. **After one molar pregnancy, the risk of having molar disease in a future gestation is about 1%.** Of 34 patients with at least two documented molar pregnancies, every possible combination of repeat molar pregnancy was observed. After two molar gestations, these 34 patients had 35 later conceptions resulting in 20 (57.1%) term deliveries, 7 (20.0%) moles (6 complete, 1 partial), 3 spontaneous abortions, 3 therapeutic abortions, 1 intrauterine fetal death, and 1 ectopic pregnancy. In six patients, the medical records indicated that the patient had a different partner at the time of different molar pregnancies (60).

Therefore, for any subsequent pregnancy, it seems prudent to undertake the following approach:

- **Perform pelvic ultrasonographic examination during the first trimester to confirm normal gestational development.**
- **Obtain an hCG measurement 6 weeks after completion of the pregnancy to exclude occult trophoblastic neoplasia.**

Pregnancies after Persistent Gestational Trophoblastic Tumor

Patients with GTT who are treated successfully with chemotherapy can expect normal reproduction in the future. Patients who were treated with chemotherapy at the authors' institution from 1965 to 2001 had 581 subsequent pregnancies that resulted in 393 term live births (67.6%), 35 preterm deliveries (6.0%), 7 ectopic pregnancies (1.2%), 9 stillbirths (1.5%), and 8 repeat molar pregnancies (1.4%) (59). First- and second-trimester

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spontaneous abortions occurred in 99 (17.0%) pregnancies. Major and minor congenital malformations were detected in 10 infants (2.3%). Primary cesarean delivery was performed in 68 (20.3%) of 335 subsequent term and preterm births from 1979 to 2001. It is particularly reassuring that the frequency of congenital anomalies is not increased, although chemotherapeutic agents are known to have teratogenic and mutagenic potential.

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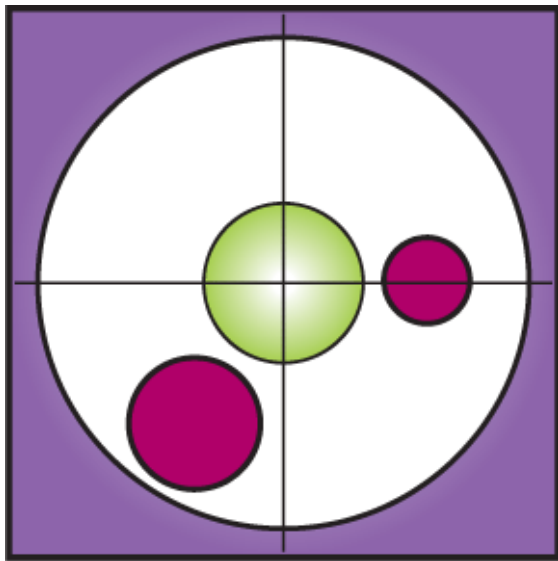
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Breast Cancer

Kristine E. Calhoun

Armando E. Giuliano



- **Breast cancer accounts for one third of cancers in women. The risk of breast cancer increases with a positive family history and the use of hormone therapy. Breast cancer may be either *in situ* (ductal carcinoma *in situ* or lobular carcinoma *in situ*) or invasive (infiltrating ductal carcinoma, infiltrating lobular carcinoma).**
- **The standard screening modalities for detection of breast cancer include yearly mammography and physical examination.**
- **Tissue diagnosis is achieved using fine-needle aspiration cytology (FNAC) or core needle biopsy (CNB). Open biopsy is performed if FNAC or CNB has not been performed or if these results are negative, equivocal, or discordant with the clinical findings.**
- **The combination of segmental mastectomy (with negative surgical margins), axillary lymph node dissection, and postoperative radiation therapy is equivalent to modified radical mastectomy for the management of**

certain patients with stages I and II breast cancer.

- **Axillary lymph node status and the number of involved nodes is the most important prognostic indicator in primary breast cancer.**
- **Adjuvant systemic therapy prolongs survival in selected breast cancer patients and is recommended for women with a greater than 10% chance of relapse within 10 years.**

Breast cancer accounts for approximately one third of all cancers in women and is second only to lung cancer as the leading cause of cancer deaths among women.

Breast cancer, however, has the highest incidence rate of all cancers. According to statistics from the American Cancer Society, 213,000 new cases of invasive breast cancer, as well as nearly 62,000 cases of *in situ* cancers, will be diagnosed during 2006 in the United States, with 41,000 women succumbing to the disease during the same period (1). Over the past 50 years, the incidence of breast cancer in the United States has increased significantly; currently one in every seven women will develop the disease during her lifetime. Fortunately, the mortality rate has declined since 1990.

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Predisposing Factors

Fewer than 1% of breast cancers occur in women younger than 25 years of age. After age 30, however, there is a sharp increase in the incidence of breast cancer. Except for a short plateau between the ages of 45 and 50 years, the incidence increases steadily with age (2).

Family History

Of women who develop breast cancer, 20% to 30% have a family history of the disease. Although any family history of breast cancer increases the overall relative risk (3), this risk is not significantly increased if the disease was diagnosed postmenopausally in a first degree or more distant relative. If a woman's mother or sister had unilateral breast cancer premenopausally, her lifetime risk of developing the disease approaches 30%, whereas a woman whose mother or sister had bilateral breast cancers premenopausally has at least a 40% to 50% lifetime risk. The increased incidence in these women is probably due to inherited oncogenes.

Approximately 5% to 10% of breast cancers have an inherited basis. All inherited genes are autosomal dominant but have variable penetrance. Men carry the gene 50% of the time. The most common mutations are the ***BRCA1*** (chromosome 17q21) and ***BRCA2*** (chromosome 13q12–13) gene deletions. **Carriers of these germline mutations have up to a 4%-per-year risk of developing breast cancer and a lifetime risk that ranges from 35% to 85% (4).** In addition, these individuals have up to a 65% risk of developing a contralateral breast cancer. The ***BRCA1*** mutation also is associated with an increased risk of ovarian and prostate cancer, whereas ***BRCA2*** carriers, although less common, demonstrate increased risks of male breast and prostate cancers. Both mutations are rare in the general public (0.1%) but are more commonly identified in Jews of Ashkenazi descent (1%–2.3%) (5). **Genetic testing is available and should be considered if there is a high likelihood that results will be positive and will be used to influence decisions regarding the clinical management of the care of the patient and her family.**

Diet, Obesity, and Alcohol

There are marked geographic differences in the incidence of breast cancer that may be related to diet. A recent meta-analysis demonstrated an association between higher intakes of total fat and an increased risk of breast cancer (6). Although a definitive relationship between total alcohol consumption and an increased risk of breast cancer has yet to be determined, high wine intake has been shown to be associated with elevated risk (7).

Reproductive and Hormonal Factors

The risk of breast cancer increases with the length of a woman's reproductive phase (8). Although early menarche has been reported among breast cancer patients, early menopause appears to protect against the development of the disease, with artificial menopause from oophorectomy lowering the risk more than early natural menopause (9). There is no clear association between the risk of breast cancer and menstrual irregularity and the duration of menses. Although lactation does not affect the incidence of breast cancer, women who have never been pregnant have a higher risk of breast cancer than those who are multiparous. Also, women who give birth to their first child later in life have a higher incidence of breast cancer than do younger primigravida women (10).

An historic well-controlled study from the Centers for Disease Control and Prevention showed that oral contraceptive use does not increase the risk of breast cancer, regardless of duration of use, family history, or coexistence of benign breast

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disease (11). However, a more recent pooled analysis from 54 epidemiologic studies showed current users of oral contraceptives had a small but significant increased risk when compared with nonusers. Ten years after discontinuation, the risk of past users declined to that of the normal population (12).

Although it was previously reported that short-term estrogen treatment for menopausal symptoms did not increase the risk of breast cancer, this belief was refuted by publication of the results of the Women's Health Initiative randomized trial. This prospective trial, involving 16,000 postmenopausal women randomly assigned to receive estrogen plus progesterone or placebo, revealed an association between hormone therapy use and the development of breast cancer. In addition, when invasive breast cancer did develop, it was diagnosed at a more advanced stage compared with tumors that developed among placebo users. Based on interim analysis, the trial was stopped early and the investigators concluded that even relatively short-term use of combined estrogen-progesterone therapy increases the development of invasive breast cancer (13). The risk demonstrated by this study must be considered when postmenopausal hormone therapy is used to treat conditions such as hot flashes and osteoporosis.

History of Cancer

Women with a history of breast cancer have a 50% risk of developing microscopic cancer and a 20% to 25% risk of developing clinically apparent cancer in the contralateral breast, which occurs at a rate of 1% to 2% per year (14). Lobular carcinoma has a higher incidence of bilaterality than does ductal carcinoma. A history of endometrial, ovarian, or colon cancer also is associated with an increased risk of subsequent breast cancer, as is a history of radiation therapy for Hodgkin's lymphoma.

Diagnosis

Breast cancer most commonly arises in the upper outer quadrant, where there is proportionally more breast tissue. Masses are most often discovered by the patient and less frequently by the physician during routine breast examination. The increasing use of screening mammography has enhanced the ability to detect nonpalpable breast abnormalities. Metastatic breast cancer is found as an axillary mass without obvious malignancy in less than 1% of cases.

The standard screening modalities of mammography and physical examination are complementary. Approximately **10% to 50% of cancers detected mammographically are not palpable, whereas physical examination detects 10% to 20% of cancers not seen radiographically** (15). The purpose of screening is to detect tumors when they are small (less than 1 cm) and have the highest potential for surgical cure. Most trials have shown a 20% to 30% reduction in breast cancer mortality for women age 50 and older who undergo annual screening mammography. Data on screening women younger than 40 years have been more controversial. **Results from the Gothenburg screening trial showed a 45% reduction in mortality for women screened between the ages of 40 and 49** (16). **Because of these findings, it is recommended that all women undergo yearly screening mammography starting at age 40, along with clinical breast examination and breast self-examination.** No other tests, including ultrasonography, computed tomography (CT) scans, sestamibi scans, positron emission tomography (PET) scans, or serum blood markers, have been shown to be effective screening modalities. Screening guidelines recommended by the American College of Radiology and the American Cancer Society are presented in Table 38.1. Recently, MRI was identified as a valuable adjunct to screening mammography for women with either a familial or genetic predisposition to breast cancer, although exact guidelines for its implementation have yet to be defined (17).

Table 38.1 Screening Recommendations

Bilateral mammograms

Beginning at age 40 yearly mammogram

Women at increased risk (positive family history, gene positive, personal history of breast cancer) should talk to their physicians about the potential benefits of starting mammography earlier than age 40, having additional imaging studies such as MRI, or having more frequent clinical exams.

Self-examination

Premenopausal 5–7 days after menstrual period monthly

Postmenopausal same day every month

Clinical breast examination

Age 20–40 exam by physician every 3 years, annually if positive history
(May do annually if there is a positive family history)

Age ≥ 40 exam by physician every year

Tumor markers CA27–29, CA15–3, not recommended as screening tests

From American Cancer Society, *Screening guides for the early detection of breast cancer*, 2003.

Unfortunately, although breast MRI is exceptionally sensitive in the detection of breast abnormalities, the technology is currently not specific enough for this imaging modality to be used for routine screening.

Masses are easier to palpate in older women with fatty breasts than in younger women with dense, nodular breasts. An area of thickening amid normal nodularity may be the only clue to an underlying malignancy. Skin dimpling, nipple retraction, or skin erosion, while obvious, are later-stage disease signs. Algorithms for the evaluation of breast masses in premenopausal and postmenopausal women are presented in Chapter 19.

When a dominant breast mass is identified, the presence of a carcinoma must be considered, and biopsy should be performed to establish a tissue diagnosis. About 30% to 40% of lesions believed clinically to be malignant will be benign on histologic examination (18). Conversely, 25% of clinically benign-appearing lesions will be malignant when biopsied (19).

Biopsy Techniques

In rare cases, it may be reasonable to perform frozen section analysis on a biopsy specimen immediately before mastectomy or other definitive surgical treatment. It is preferable, however, for the patient to be involved in the planning of her therapy. In most instances, initial biopsy is better followed by definitive treatment at a later date. This approach allows the physician to discuss alternative forms of surgical therapy with the patient who has a malignancy. It also gives the patient an opportunity to obtain a second opinion before undergoing definitive treatment.

Fine-needle Aspiration Cytology

Fine-needle aspiration cytology (FNAC) is usually performed on palpable lesions or under ultrasound guidance using a 20- or 22-gauge needle. The technique has a high level of diagnostic accuracy, with low false-negative rates and rare, but persistent, false-positive results (20). In most reported series, **false-negative rates range from 10% to 15%, and false-positive rates are generally less than 1%, whereas insufficient specimens account for about 15% of samples** (21). If a mass appears to be malignant on physical

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examination, mammography, or both, FNAC cytology results can be used for definitive diagnosis. Negative FNAC results do not exclude malignancy and should be evaluated by either a core needle or traditional excisional biopsy for suspicious lesions. In younger women, it is prudent to monitor a benign-appearing mass for one or two menstrual cycles. Confirmation of a clinically apparent fibroadenoma with FNAC can serve as the basis for observational follow-up without excision.

Core Needle Biopsy

Core needle biopsy can be performed on both palpable and nonpalpable breast masses. **Performing a core biopsy instead of FNAC on a palpable lesion has the advantage of obtaining more tissue for diagnostic purposes, including tests for estrogen and progesterone receptors and Her2/*neu*.** Core biopsy of nonpalpable breast lesions usually is performed using mammographic or ultrasonographic guidance. Mammographic units with computerized stereotactic modifications can be used to localize abnormalities and perform CNB without surgery. **Under mammographic guidance, a biopsy needle is inserted into the lesion and a core of tissue is removed for histologic examination.** Devices with suction assistance are often used to increase the volume of tissue removed for evaluation. A titanium clip often is used to mark the biopsy site and serve as a guide should further excision be required. Ultrasonography may also be used to perform core biopsy on a nonpalpable lesion. Because it is less invasive and less expensive than

open mammographic localization biopsy, CNB is preferred for accessible lesions. If a definitive diagnosis is not established, these procedures must also be followed by open biopsy.

Open Biopsy

Open biopsy may be performed if FNAC or CNB has not been performed or if needle biopsy results are negative, equivocal, or discordant with the clinical findings. **An unequivocal histologic diagnosis of cancer should be obtained before treatment of breast cancer is undertaken.** Cytologic diagnosis may be relied on if the mass clinically or mammographically appears to be malignant.

Open biopsy can be performed in the outpatient setting with local anesthesia in the following manner:

- The patient is positioned and the location of the mass confirmed.
- Local anesthesia is used to infiltrate the skin and subcutaneous tissue surrounding the palpable mass.
- The skin is incised directly over the mass. Placement of this incision is critical. It should be situated in such a way that it can be excised with an ellipse of skin should the patient require a subsequent mastectomy or placed cosmetically so that partial mastectomy can be performed through it successfully. Para-areolar incisions are appropriate only for lesions in proximity to the nipple-areolar complex.
- The mass is gently grasped with Allis forceps or with a stay suture and moved into the operative field.
- The mass should be excised completely whenever possible. Larger lesions that are difficult to totally excise can be incised for diagnostic purposes only. When an incisional biopsy is performed, a frozen section should be obtained to confirm that appropriate tissue for diagnosis is present. Such masses, however, are preferably sampled with FNAC or CNB, with incisional biopsy rarely indicated.
- Once the mass is removed, hemostasis is achieved and the incision is closed. A cosmetically superior result will be achieved if the deep breast parenchyma is not

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reapproximated. The most superficial subcutaneous fat can be reapproximated with fine absorbable sutures, and the skin can be closed with a subcuticular suture and adhesive strips.

Image-Guided Localization Biopsy

Biopsy of nonpalpable lesions is a potentially difficult procedure that requires close cooperation between the surgeon and radiologist. Using ultrasonographic or mammographic guidance, a needle or specialized wire is placed into the breast parenchyma at or near the site of the suspected abnormality. Some mammographers will also inject a biologic dye into the breast parenchyma to assist localization further. The surgeon reviews the films and localizes the abnormality with respect to

the tip of the wire or needle. Alternatively, the surgeon will perform ultrasonography intraoperatively to directly localize the lesion. An incision is made directly over the abnormality, and a small portion of the breast tissue suspected of containing the abnormality is excised. For mammographically detected lesions, a specimen radiograph is obtained to ensure that the abnormality has been recovered. Often, the radiologist can place a needle in the specimen at the site of the abnormality to facilitate histologic evaluation and ensure that the pathologist examines the site of the abnormality.

Pathology and Natural History

Breast cancer may arise in the intermediate-sized ducts, terminal ducts, or lobules. In most cases, the diagnosis of lobular and intraductal carcinoma is based more on histologic appearance than site of origin. The cancer may be either *in situ* (ductal carcinoma *in situ* or lobular carcinoma *in situ*) or invasive (infiltrating ductal carcinoma, infiltrating lobular carcinoma). Morphologic subtypes of infiltrating ductal carcinoma include scirrhous, tubular, medullary, and mucinous carcinoma.

True invasive ductal carcinoma accounts for 80% of all invasive tumors, with the final 20% split evenly between lobular carcinoma and special variants of infiltrating ductal carcinoma (22). Mammographically, invasive ductal cancers are characterized by a stellate density or microcalcifications. Macroscopically, gritty, chalky streaks are present within the tumor that most likely represent a desmoplastic response. Finally, invasion of the surrounding stroma and fat, with a fibrotic, desmoplastic reaction surrounding the invasive carcinoma, generally are present.

Special types of infiltrating ductal carcinoma are uncommon and typically account for nearly 10% of all invasive cancers. Medullary carcinoma, which accounts for 5% to 8% of breast carcinomas, arises from larger ducts within the breast and has a dense lymphocytic infiltrate. The tumor appears to be a slower growing and less-aggressive malignancy than other forms of carcinoma. Even when axillary disease is present, the prognosis with medullary carcinoma is better than that of other variants of invasive ductal carcinoma. **Mucinous (colloid) carcinoma accounts for 5% of all breast cancers.**

Grossly, areas of the tumor may appear mucinous or gelatinous, whereas microscopically they are relatively acellular. Infiltrating comedo carcinoma accounts for less than 1% of all breast malignancies and is an invasive cancer characterized by foci of necrosis that exude a comedonecrosislike substance when biopsied. Usually, comedocarcinomas are *in situ* malignancies. Papillary carcinoma is predominantly a noninvasive ductal carcinoma; when invasive components are present, it should be specified as invasive papillary carcinoma.

Tubular carcinoma, a well-differentiated breast cancer that accounts for 1% to 2% of all malignant breast neoplasms, tends to have a better prognosis than infiltrating ductal carcinoma and rarely metastasizes to axillary lymph nodes. Finally, **adenoid cystic carcinomas are extremely rare breast tumors that histologically are similar to those seen in the salivary glands.** They generally are well differentiated cancers that are slow to metastasize.

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Growth Patterns

The growth potential of breast cancer and the patient's resistance to malignancy vary widely with the individual and the stage of disease. **The doubling time of breast cancer ranges from several weeks for rapidly growing tumors to months or years for slowly**

growing lesions. If the doubling time of a breast tumor was constant and a tumor originated from one cell, a doubling time of 100 days would result in a 1-cm tumor in about 8 years (Fig. 38.1) (23). During the preclinical phase, tumor cells may be circulating throughout the body. Because of the long preclinical tumor growth phase and the tendency of infiltrating lesions to metastasize early, many clinicians view breast cancer as a systemic disease at the time of diagnosis. Although cancer cells may be released from the tumor before diagnosis, variations in the tumor's ability to grow in other organs and the host's response to tumor cells may inhibit dissemination of the disease. Many women with breast cancer can be treated successfully with surgery alone, and some patients have been cured even in the presence of palpable axillary disease. Thus, a pessimistic attitude that breast cancer is systemic and incurable at diagnosis is unwarranted.

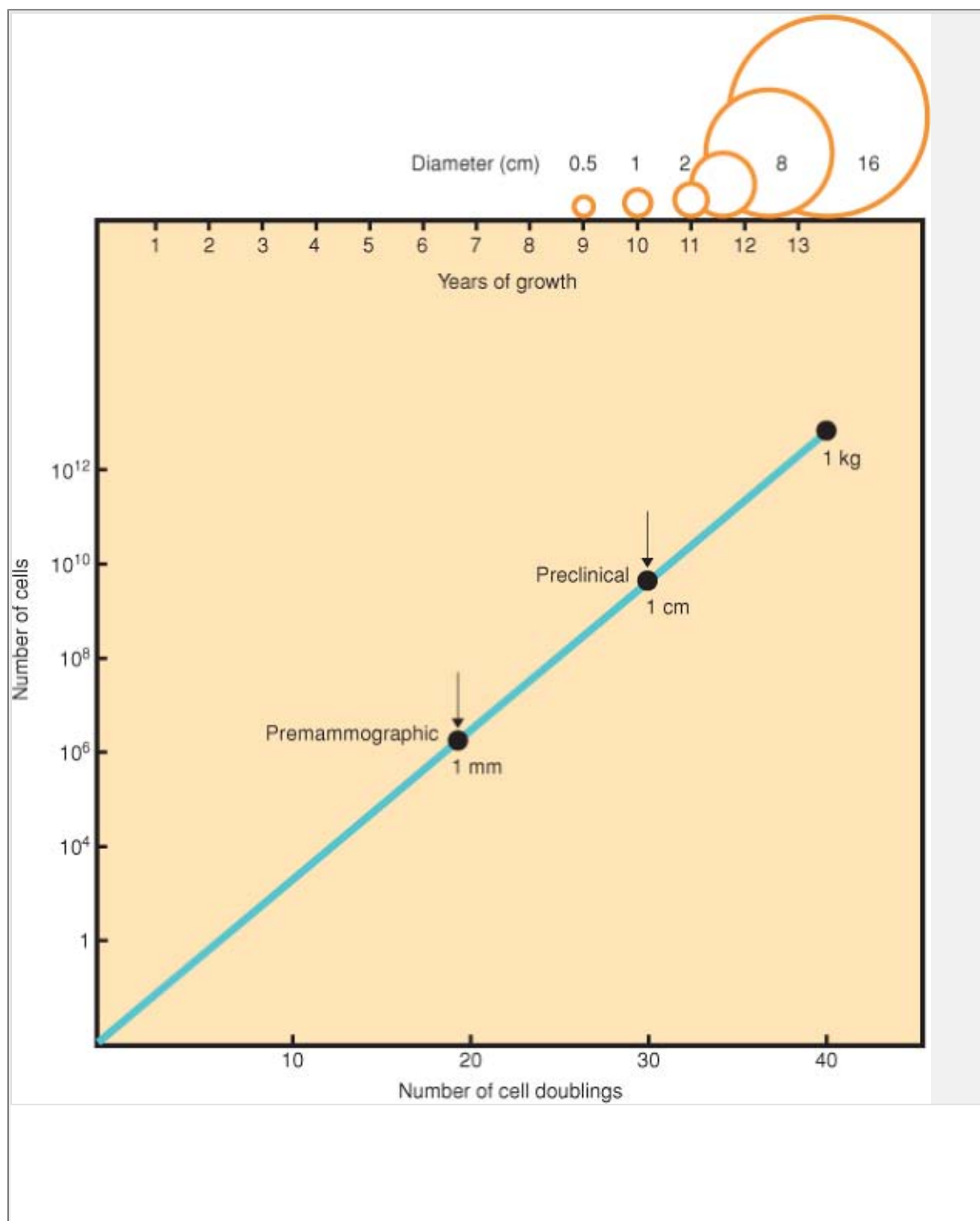


Figure 38.1 Growth rate of breast cancer indicating long preclinical phase. (From Gullino PM. Natural history of breast cancer: progression from hyperplasia to neoplasia as predicted by angiogenesis. *Cancer* 1977;39:2699. with permission.)

Table 38.2 Tumor–Nodes–Metastasis (TNM) System for Staging of Breast Cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T₀	No evidence of primary tumor
T_{is}	Carcinoma <i>in situ</i>
T_{is} (DCIS)	Ductal carcinoma <i>in situ</i>
T_{is} (LCIS)	Lobular carcinoma <i>in situ</i>
T_{is} (Paget)	Paget disease of the nipple with no tumor
T₁	Tumor 2 cm or less in greatest dimension
T_{1mic}	Microinvasion 0.1 cm or less in greatest dimension
T_{1a}	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T_{1b}	More than 0.5 cm but not more than 1 cm in greatest dimension
T_{1c}	More than 1 cm but not more than 2 cm in greatest dimension
T₂	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T₃	Tumor more than 5 cm in greatest dimension
T₄	Tumor of any size with direct extension to chest wall or skin
T_{4A}	Extension to chest wall, not including pectoralis muscle
T_{4B}	Edema (including <i>peau d'orange</i>) or ulceration of the skin of breast or satellite skin nodules confined to same breast
T_{4C}	Both T _{4A} and T _{4B}
T_{4D}	Inflammatory carcinoma
Lymph node (N)	
Clinical	
N X	Regional lymph nodes cannot be assessed (e.g., previously removed)
N₀	No regional lymph node metastasis
N₁	Metastasis to movable ipsilateral axillary lymph node(s)
N₂	Metastases to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent ipsilateral mammary nodes in the absence of clinically evident axillary node metastasis
N_{2a}	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N_{2b}	Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N₃	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph nodes and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement

N_{3a}	Metastasis in ipsilateral infraclavicular lymph nodes
N_{3b}	Metastasis in ipsilateral internal mammary lymph nodes and axillary lymph nodes
N_{3c}	Metastasis in ipsilateral supraclavicular lymph node(s)
Pathologic classification (pN)	
pN X	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN₀	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical [IHC] or molecular methods but which may be verified on H&E stains)
pN₀₍₋₎	No regional lymph node metastasis histologically, negative IHC
pN_{0(i+)}	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN_{0(mol-)}	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
pN_{0(mol+)}	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
pN₁	Metastasis in 1 to 3 axillary lymph node(s), and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN_{1mic}	Micrometastasis (>0.2 mm, none >2.0 mm)
pN_{1A}	Metastasis in 1 to 3 axillary lymph node(s)
pN_{1B}	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN_{1c}	Metastasis in 1 to 3 axillary lymph node(s), and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
PN₂	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
PN_{2a}	Metastasis in 4 to 9 axillary lymph nodes (at least 1 tumor deposit >2.0 mm)
PN_{2b}	Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
PN₃	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary nodes in the presence of 1 or more positive axillary nodes; or in more than 3 axillary nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
PN_{3a}	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis in infraclavicular lymph nodes
PN_{3b}	Metastasis in clinically apparent ipsilateral internal mammary nodes in the presence of 1 or more positive axillary nodes; or in more than 3 axillary nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
PN_{3c}	Metastasis in ipsilateral supraclavicular nodes
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed

M₀	No distant metastasis
M₁	Distant metastasis
From Greene FL, Page DL, Fleming ID, et al. , eds. Breast. In <i>AJCC cancer staging manual</i> , 6th ed. New York, NY: Springer, 2002:237–239.	

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A more realistic approach may be to view breast cancer as a two-component disease involving the breast and the body as a whole. Although the primary breast tumor and issues of local control must be managed, the possibility of systemic metastases with their life-threatening consequences should not be overlooked.

Although breast cancer can metastasize to any organ, involvement of bone, lungs, or liver occurs in up to 85% of women who develop distant disease (24,25). In addition to these sites, invasive lobular carcinoma is known to disseminate to the abdominal viscera, uterus, ovaries, and peritoneal surfaces.

Staging

After the diagnosis of breast cancer has been definitively established, the clinical stage of the disease should be determined. The Columbia Clinical Staging System was used historically (26) but has been replaced by the tumor–nodes–metastases (TNM)

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system of the American Joint Committee on Cancer (27). The TNM system allows both preoperative clinical staging and postoperative pathologic staging to be determined (Tables 38.2 and 38.3).

	<i>TNM Classification^a</i>		
	<i>Tumor</i>	<i>Node</i>	<i>Metastasis</i>
Stage 0	Tis	N ₀	M ₀
Stage I	T ₁	N ₀	M ₀
Stage IIa	T ₀	N ₁	M ₀
	T ₁	N ₁	M ₀
	T ₂	N ₀	M ₀
IIb	T ₂	N ₁	M ₀
	T ₃	N ₀	M ₀
Stage IIIa	T ₀	N ₂	M ₀
	T ₁	N ₂	M ₀
	T ₂	N ₂	M ₀
	T ₃	N ₁	M ₀
	T ₃	N ₂	M ₀
IIIb	T ₄	N ₀	M ₀
	T ₄	N ₁	M ₀

	T ₄	N ₂	M ₀
IIIc	Any T	N ₃	M ₀
Stage IV	Any T	Any N	M ₁

^aT₁ includes T_{1mic}.

From **Greene FL, Page DL, Fleming ID, et al.**, eds. Breast. In *AJCC cancer staging manual*, 6th ed. New York, NY: Springer, 2002:239.

Treatment

Preoperative Evaluation

The extent of the preoperative workup varies with the initial stage of the disease (28).

For most patients with small tumors, clinically negative lymph nodes, and no evidence of metastasis (TNM stage I), the preoperative evaluation should consist of bilateral mammography, chest radiography, complete blood count, and screening blood chemistry tests. Bone, CT, and MRI scanning are unnecessary unless there are symptoms or abnormal blood chemistry levels to suggest the existence of bone or intra-abdominal involvement. For patients with clinical stage II, node-positive disease, a bone scan is recommended, but CT scan of the abdomen is not necessary unless symptoms or laboratories suggest liver disease. Patients with clinical stage III or stage IV disease should undergo both bone and liver scanning.

Radical Mastectomy

Traditionally, the treatment of breast cancer has been surgical, but the type of procedure has remained a controversial and highly emotional issue. During the nineteenth century, surgical treatment of breast cancer was haphazard, varying from local excision alone to total mastectomy. The radical mastectomy was based on the principle that breast

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carcinoma was a locally infiltrative process that spread in a stepwise fashion from breast, to nodes, to distant sites (29). Thus, **radical mastectomy removes the entire breast, the underlying pectoral muscles, and the contiguous axillary lymph nodes in continuity (30)** (Fig. 38.2A). A report of 51 years of experience with radical mastectomy, which included 1,036 patients with a follow-up of 47 years, is thus far unequaled in evaluating any single method of treating breast cancer (31).

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Figure 38.2 Appearance of breast after radical mastectomy (A) versus modified mastectomy (B). (From **Chang SS, Haigh PI, Giuliano AE**. Breast disease. In: **Berek JS, Hacker NF**, eds. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:648, with permission.)

During the twentieth century, extensions and modifications of the radical mastectomy were devised that involved removal of more local and regional tissue. At one time, supraclavicular

lymph node dissections were considered a routine component of surgical treatment (32). In addition, supraclavicular, mediastinal, and internal mammary lymph node dissections were performed (33).

An *en bloc* internal mammary lymph node dissection was added to the standard radical mastectomy in the 1960s (34). This technique became popular and is the operation commonly referred to as the *extended radical mastectomy*. Unfortunately, extended radical mastectomy did not enhance overall survival rates (35), because only 3% to 5% of patients with negative axillary nodes will have involvement of internal mammary nodes. Locally destructive surgery is not justified, however, based on current understanding of the biologic behavior of breast cancer.

Modified Radical Mastectomy

In contrast to radical mastectomy, modified radical mastectomy preserves the pectoralis major muscle (36,37) (Fig. 38.2B). The breast is removed in a manner similar to that of radical mastectomy, but neither the axillary lymph node dissection nor the skin excision is as extensive. Consequently, there is no need for skin grafting. Although there are no differences in survival rates between radical and modified radical mastectomy, the latter procedure has a better functional outcome and a superior cosmetic result (38). Modified radical mastectomy has therefore replaced radical mastectomy in the United States.

Total Mastectomy

Total mastectomy involves removal of the entire breast, nipple, and areolar complex without resection of the underlying muscles or intentional excision of axillary lymph nodes. Low-lying lymph nodes, however, in the upper outer portion of the breast and low axilla often are excised. Total mastectomy has local control rates comparable with those of radical or modified radical mastectomy but has a higher risk of axillary recurrence. Regional recurrence will occur in at least 15% to 20% of patients treated with total mastectomy alone.

Postmastectomy Radiation Therapy

McWhirther developed the combination of total mastectomy followed by radiation (39). Many have advocated adjuvant radiation therapy used in combination with various operative procedures. Unfortunately, studies claiming improvements in overall survival usually are flawed by the use of historical controls and inaccurate preoperative staging. Classic trials, both prospective randomized and historical control studies, have showed that adjuvant radiation therapy improves local control but not overall survival rates (40,41,42,43). In a prospective randomized trial performed by the National Surgical Adjuvant Breast Project (NSABP), the roles of postoperative radiation therapy and axillary treatment were examined. Patients were randomly assigned to either total mastectomy, radical mastectomy, or total mastectomy with radiation therapy. This trial showed no difference in survival among the three treatment arms, whereas radiation therapy and axillary treatment improved local and regional control. Twenty-five-year follow-up data continue to support these conclusions (44).

Three randomized control studies from the 1990s showed that postmastectomy radiation therapy reduced the risk of local-regional failure by 20% and produced an absolute survival benefit of 10% at 10 years among women with stage II to III breast cancer, regardless of menopausal status (45,46,47). More recently, additional trials challenged the need for postmastectomy radiation among women with only one to three involved axillary nodes and T₁ or T₂ primary tumors. These studies showed adequate

local-regional control rates with mastectomy and chemotherapy alone (48,49,50).

Current guidelines from the American Society of Clinical Oncology recommend postmastectomy

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radiation therapy for women with T₃ (>5 cm) primary tumors and four or more positive axillary lymph nodes (51).

Breast Conservation Therapy with or without Radiation Therapy

Radiation therapy alone, without excision of the tumor, is associated with a high local failure rate (52,53,54,55), as is local excision without radiation. Throughout the last quarter of the twentieth century, a paradigm shift occurred in the surgical management of breast cancer. Data from the NSABP B-04 trial, for which 25-year follow-up exists, established the equivalency of radical versus total mastectomy with regards to overall survival (56). Shortly after initiation of the B-04 trial, a number of studies were designed to evaluate the efficacy of breast preservation among women with early-stage breast cancers. **The Milan trial, a major prospective randomized trial that began accruing patients in 1973, compared treatment with either radical mastectomy or a combination of quadrantectomy, axillary lymph node dissection, and postoperative radiation therapy.** In total, 701 clinically node-negative patients with noncentrally located, small tumors (<2 cm) (T₁ N₀ M₀) were enrolled. **After 20 years of follow-up, there continues to be no statistically significant difference between the two groups in either local control or overall survival rates (57).**

At nearly the same time, **in the NSABP B-06 trial, patients with early breast cancer (stage I or stage II, T₁ or T₂, and N₀ or N₁) were randomized to modified radical mastectomy, segmental mastectomy (lumpectomy), and axillary lymph node dissection, or segmental mastectomy, axillary lymph node dissection, and postoperative radiation therapy.** Unlike the quadrantectomy performed in the Milan study, segmental mastectomy consists of removing only the tumor and a small rim of normal surrounding tissue, yielding cosmetically superior results (Fig. 38.3). A total of 1,843 women were enrolled, with the lowest local recurrence rate seen among patients treated with segmental mastectomy and postoperative radiation therapy. Although the addition of radiation clearly

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improved the local control rate, no significant differences in overall survival or disease-free survival rates were detected among the three treatment arms; there was a trend, however, in favor of patients who received radiation. **This NSABP study established, now with 25-year follow-up, that the combination of segmental mastectomy (with negative surgical margins), axillary lymph node dissection, and postoperative radiation therapy is as effective as modified radical mastectomy for the management of patients with stage I and II breast cancer (58).** A number of additional studies also demonstrated no decrease in overall survival among women being treated with breast preservation therapy (59,60,61).



Figure 38.3 Appearance of breast after lumpectomy, axillary dissection, and radiation therapy. (From **Chang SS, Haigh PI, Giuliano AE.** Breast disease. In: **Berek JS, Hacker NF,** eds. *Practical gynecologic oncology*, 4th ed. Philadelphia, PA: Williams & Wilkins, 2005:650, with permission.)

Axillary lymph node status and the number of involved nodes is the most important prognostic indicator for patients with primary breast cancer (62). For these reasons, axillary lymphadenectomy traditionally was used to detect and quantify the extent of nodal metastasis (63). Before the introduction of sentinel lymph node dissection in the 1990s, axillary lymph node dissection was performed routinely on all patients with early breast cancer. Although axillary dissection is associated with a very low risk of regional recurrence (1%–3%), the rate of acute complications is as high as 30% (64). Similarly, the risk of chronic lymphedema ranges from 6% to as high 30% (65). Limiting the dissection to level I nodes or random sampling is associated with unacceptably high false-negative rates and should not be done (66). Only one third of patients with a clinically negative axilla will be found to have nodal metastasis after histopathologic examination of all harvested lymph nodes (67). This means that two thirds of patients will be exposed to the morbidity of axillary lymph node dissection without proven benefit when performed routinely in the presence of invasive breast cancer.

In 1991, intraoperative lymphatic mapping and sentinel lymph node dissection were introduced to address these problems (68). The concept behind sentinel lymph node dissection is best described by the definition of a sentinel node. The sentinel node is the lymph node that has the greatest potential to harbor metastasis if axillary disease is present. The sentinel lymph node dissection thus accurately predicts the status of the entire nodal basin. Removing only one or two lymph nodes can accurately stage the axilla with minimal morbidity. Numerous investigators have demonstrated that, with proper training, sentinel lymph node dissection identification rates range from 90% to 99%, with false-negative rates of less than 5% found in most large studies (69). **In one study of 107 patients with T₁ and T₂ breast cancer who underwent sentinel lymph node dissection followed by axillary**

lymph node dissection, the sentinel node was successfully identified in 100 patients (93.5%). There were no false-negative results, and the sentinel node accurately predicted axillary status in all 100 patients.

The technique of sentinel lymph node dissection has been validated by a number of authors using a variety of techniques (70,71). The information obtained from sentinel lymph node dissection appears to be equivalent to that of axillary lymph node dissection in the trials conducted to date. One prospective study demonstrated that in node-negative patients undergoing sentinel lymph node dissection, only the recurrence rate in the axilla was zero at a median follow-up of 39 months (72). An additional randomized trial demonstrated sentinel node biopsy to be both safe and accurate when compared with axillary dissection, with fewer complications and no axillary recurrences among the sentinel node trial arm (73). **This degree of accuracy in predicting axillary metastasis, combined with its very low morbidity rate, makes sentinel lymph node dissection the preferred procedure for staging the axilla in breast cancer today.**

Adjuvant Systemic Therapy

For many patients, local and regional control of breast cancer is achieved with surgery and radiation therapy alone. About 90% of patients will never experience an in-breast recurrence; these patients, however, may still develop metastatic disease. The goal of adjuvant

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systemic therapy is to eliminate occult metastases during the early postoperative period and thus reduce the risk of local and distant recurrence (74).

Adjuvant systemic therapy will prolong survival in selected breast cancer patients.

In patients with favorable tumors and a low risk of recurrence and subsequent death, however, such as those with node-negative cancers smaller than 1 cm or node-negative cancers smaller than 2 cm with grade 1 histology, this benefit is small and may not justify the risks of systemic therapy. **Adjuvant systemic therapy reduces the odds of death by 25% per year in both node-negative and node-positive patients** (75). Because this risk reduction is relatively constant, patients with favorable, node-negative disease have a much smaller absolute benefit compared with patients who have higher-risk, node-positive disease. For patients with node-negative disease, the absolute benefit may be minimal versus 10% to 20% for those with nodal involvement.

Cytotoxic chemotherapy and hormonal therapy have inherent risks that must be considered when treatment decisions are made. Although there are many known acute side effects with current standard regimens, there is growing evidence that patients who undergo chemotherapy report more frequent chronic neurocognitive deficits than do untreated controls (76). The impact of these deficits remains undefined. Similarly, systemic therapy with *tamoxifen* has been associated with an increased incidence of uterine cancer, vaginal dryness, and hot flashes, whereas aromatase inhibitors have been linked to osteoporosis and musculoskeletal symptoms. Choosing those patients who should receive adjuvant therapy can be a difficult decision that often entails analyzing a variety of prognostic and predictive factors, identifying patients at risk for recurrence, and quantifying that risk. **Based on available data, adjuvant chemotherapy is currently recommended for women with greater than a 10% chance of relapse within 10 years.** The choice of therapy generally depends on an evaluation of specific risk factors. Recently, gene assays such as the Oncotype DX have been introduced to help identify those estrogen receptor-positive, lymph node-negative patients who will benefit most from systemic chemotherapy. This test, which calculates a recurrence risk score for each individual, allows the treating physician to determine the average rate of distant disease at 10 years and make treatment

recommendations based on this risk (77).

Prognostic Indicators

Factors that determine each patient's risk of recurrence include nodal involvement, tumor size, estrogen and progesterone receptor status, nuclear grade, histologic type, proliferative rate, and biologic markers such as Her2/*neu* status. These prognostic factors and their effects on recurrence are summarized in Table 38.4. Patients with high-risk prognostic factors are more likely to benefit from adjuvant cytotoxic or hormonal therapy and usually are offered such treatment.

Patients with lymph node metastasis have a higher risk of recurrence than patients with node-negative disease. The 10-year survival rate for women with palpable metastatic axillary lymph nodes who fail to receive systemic therapy is only about 50% to 60%. The number of lymph nodes involved and the presence of extracapsular invasion are important indicators of poor prognosis.

Another prognostic indicator of relapse is primary tumor size. In an evaluation of 767 patients with node-negative disease who underwent radical or modified radical mastectomy without adjuvant chemotherapy, the relapse rate in patients with tumors larger than 1 cm or special tumor types larger than 3 cm (tubular, mucinous, or papillary) was 27% at 10 years, compared with 9% for tumors smaller than 1 cm (78).

Hormone receptor status is an important predictor not only of long-term prognosis but also of response to endocrine therapy. Several studies demonstrated that patients with positive estrogen and progesterone receptor status have improved overall

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survival (79,80). Receptor status should be known when determining the need for and choice of adjuvant therapy. Histologic grade also appears to predict overall survival. Patients with well-differentiated tumors tend to have more favorable outcomes than those with poorly differentiated ones (Table 38.5). In a British study of 1,168 women, histologic grade, along with tumor size and lymph node status, was an independent predictor of overall survival at 10 years (81).

Table 38.4 Prognostic Factors in Node-negative Breast Carcinoma

<i>Factor</i>	<i>Increased Risk of Recurrence</i>
Size	Larger tumors
Histologic grade	High-grade tumors
DNA ploidy	Aneuploid tumors
Labeling index	High index (>3%)
S phase fraction	High fraction (>5%)
Lymphatic-vascular invasion	Present
Cathepsin D	High levels
HER-2/<i>neu</i> oncogene expression	High expression
Epidermal growth factor	High levels

From **Giulino AE**. Breast. In: **Tierney LM, McPhee SJ, Papadakis MA**, eds. 1995 current medical diagnosis and treatment. Norwalk, CT: Appleton & Large, 1995;607.

Finally, the possible roles of specific tumor markers in predicting which patients will respond to chemotherapy regimens have been investigated. The most thoroughly researched of these markers is HER-2/*neu*. In an NSABP study, patients with HER-2/*neu* overexpression who were not treated with *anthracycline*-based regimens fared worse (82). Another study showed that the addition of *trastuzumab* (*Herceptin*), an antibody directed against the HER-2/*neu*

receptor, significantly increased the response rate to therapy over standard chemotherapy alone in the presence of metastatic disease (83). At the 2005 meeting of the American Society of Clinical Oncology, **data were reported from trials investigating the adjuvant use of Herceptin for women with early-stage Her2/neu breast cancers. Significant improvements in disease-free survival were reported for those women receiving Herceptin** (84), suggesting that its routine use as an adjuvant therapy is inevitable.

Table 38.5 Year Survival According to Stage of Breast Cancer

<i>AJCC Stage</i>	<i>5-Year Survival (%)</i>	<i>10-Year Survival (%)</i>
Stage 0	95	90
Stage I	85	70
Stage IIa	70	50
IIb	60	40
Stage IIIa	55	30
IIIb	30	20
Stage IV	5–10	2
All	65	30

AJCC, American Joint Committee on Cancer.

From **Giuliano AE**. Breast. In: **Tierney LM, McPhee SJ, Papadakis MA**, eds. *2005 Current medical diagnosis & treatment*. New York, NY: Lange Medical Books/McGraw Hill, 2005:700.

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Systemic Regimens

Based on the results of more than 100 prospective, randomized trials examining the role of adjuvant chemotherapy in breast cancer, a variety of systemic regimens have emerged. Systemic therapy includes cytotoxic agents and hormonal agents, used alone or in combination. Following is a brief description of the more commonly used regimens. Initially, trials involved a single perioperative course of chemotherapy aimed at eradicating circulating tumor cells. The Nissen-Meyer study from Norway showed that a single course of *cyclophosphamide* improved overall survival rates (85). Subsequently, numerous trials demonstrated the benefit of adjuvant chemotherapy for certain subgroups of patients (86). In the initial NSABP adjuvant trial, a 2-year course of *melfhalan* was shown to be superior to no treatment (87), and further trials demonstrated enhanced beneficial effect with the use of multiple drugs as well as with the combination of hormonal manipulation with chemotherapy (88).

Historically, the most frequently used adjuvant combination chemotherapy has been CMF: *cyclophosphamide* (C), *methotrexate* (M), and *5-fluorouracil* (5-FU). In the original study by Bonadonna et al., patients with positive axillary lymph nodes were randomized to receive either 12 monthly cycles of CMF or no therapy after radical mastectomy (89). A statistically significant benefit was found with CMF treatment for premenopausal patients, especially those with one to three positive nodes. A subsequent study showed six cycles of CMF to be as effective as 12 cycles (90). Interestingly, no significant effect was seen for postmenopausal women, which was probably related in part to the fact that these women were less likely to tolerate the full course of therapy (91). **After 20 years of follow-up, this trial demonstrated a persistent survival advantage for premenopausal women receiving CMF adjuvant therapy (92). In a later study involving node-negative, estrogen receptor-negative breast cancer patients, after 12 years of follow-up, 71% of patients treated with adjuvant CMF remained disease free compared with 48% in**

the control group, regardless of menopausal status (93).

Currently, *anthracyclines* (A) are more commonly used in the adjuvant and metastatic treatment of breast cancer than any other agents. A large randomized NSABP study compared CMF with AC regimens in node-positive patients and found similar treatment outcomes among both groups. The AC regimen, however, was preferred because of its shorter duration (four cycles for 3 months versus six cycles for 6 months) and better tolerance (94).

Taxanes are also being used in a variety of multiple-agent chemotherapy regimens because of their demonstrated activity in metastatic breast cancer patients (95). **In a randomized trial of 3,170 node-positive patients who received four cycles of AC followed by four cycles of paclitaxel for 4 weeks or no additional therapy, survival rates improved from 84% to 87% in the treated group after 36 months of follow-up.** Benefits were similar in both premenopausal and postmenopausal women (96). Although the role of taxanes in the adjuvant setting for women with node-negative disease has yet to be definitively defined, early results suggest an improvement in overall survival when taxanes are used in the treatment of women with early-stage breast cancer (97).

Neoadjuvant Systemic Therapy

The use of neoadjuvant chemotherapy traditionally was limited to those individuals with either inoperable locally advanced or inflammatory breast cancers. The goal of preoperative systemic therapy was to convert inoperable patients into resectable candidates on the basis of pathologic and clinical responses (98). More recently, indications for neoadjuvant chemotherapy have been broadened to include individuals presenting with large operable tumors who desire to attempt breast preservation instead of mastectomy. Recent reports indicate that breast conservation therapy is possible and that low rates of in-breast or local-regional recurrences occur when neoadjuvant chemotherapy results in clinical and pathological tumor downstaging (99). In addition to large, operable tumors, neoadjuvant therapy continues to have a role in the treatment of inflammatory breast cancers and those presenting in a locally advanced state.

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Hormonal Therapy

Hormonal manipulation with *tamoxifen* or an aromatase inhibitor, used alone or in combination with a cytotoxic regimen, is beneficial in select groups of women. *Tamoxifen*, an estrogen analogue, offers substantial benefits in both premenopausal and postmenopausal women. Taken at a dose of 20 mg per day for 5 years, *tamoxifen* reduces the annual risk of recurrence by about 50% and the annual risk of death by about 25%. These benefits were seen in women with estrogen receptor–positive disease regardless of chemotherapy treatment (100).

***Tamoxifen*, when used in combination with cytotoxic chemotherapy, improves survival in women with positive axillary lymph nodes and positive estrogen receptor expression (101).** In patients with node-negative, estrogen receptor–positive disease, the addition of *tamoxifen* to chemotherapy improved disease-free survival rates after 5 years of follow-up (102). In NSABP study B-14, 2,644 patients with estrogen receptor–positive tumors and no axillary metastases were randomized to either *tamoxifen* (10 mg orally twice daily for 5 years) or a placebo control. After a 4-year median follow-up, the disease-free survival rate for the 1,318 patients treated with *tamoxifen* was 82% compared with 77% for the 1,326 patients treated with placebo ($P = 0.00001$), again regardless of menopausal status.

The Early Breast Cancer Trialists' Collaborative Group performed a meta-analysis

of adjuvant systemic therapy for breast cancer. They analyzed randomized trials involving adjuvant systemic hormonal, cytotoxic, or immune therapy administered to more than 75,000 women with stage I or II carcinoma. **The investigators concluded that for postmenopausal women with estrogen receptor–positive tumors, *tamoxifen* daily for at least 2 years had a significant beneficial effect on disease-free survival rates, with these effects lasting up to 10 years. The incidence of both carcinoma in the contralateral breast and death rate from heart disease decreased.**

In addition to *tamoxifen*, aromatase inhibitors have been approved for use in the adjuvant treatment of patients with estrogen-receptor positive cancers.

Aromatase inhibitors act by inhibiting the aromatase enzyme, thus blocking the conversion of androgens into estrogens. These drugs should be used only in postmenopausal patients or premenopausal women who have undergone chemical ovarian suppression or oophorectomy. Although aromatase inhibitors cause fewer episodes of thrombotic events, hot flashes, and endometrial cancers, musculoskeletal symptoms and osteoporosis are more commonly encountered among aromatase inhibitor users than those taking *tamoxifen*. Results from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial showed overall lower recurrence rates, as well as fewer contralateral tumors, among women treated with *Arimidex* alone after 68 months of follow up (103). Based on these results, **aromatase inhibitors are now often offered as a first-line treatment option for adjuvant therapy.** In addition, **recent research suggests that conversion of patients from *tamoxifen* to an aromatase inhibitor, such as *Femara*, after 2.5 or 5 years may improve survival, although concurrent use of the two agents offers no benefit (103,104).**

General Recommendations

Adjuvant systemic therapy lowers the incidence of recurrence by 25% to 30%. It is important to understand that the proportional reduction in risk of relapse is relatively constant regardless of absolute risk (105) (Table 38.6). As mentioned earlier, adjuvant cytotoxic chemotherapy appears to affect the natural history of patients with either axillary node-negative or node-positive breast cancer. All high-risk patients with node-negative disease are now considered candidates for adjuvant cytotoxic therapy.

In postmenopausal, estrogen receptor–positive women, chemotherapy is about one half as effective as *tamoxifen* in the adjuvant setting (106). For most postmenopausal women with hormone-responsive disease (estrogen- and progesterone-responsive positivity),

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including node-positive patients, hormonal therapy alone may be adequate treatment. High-risk patients with hormone-resistant disease benefit from cytotoxic systemic therapy. Caution should be exercised when using chemotherapeutic agents. Patients in whom the risk of recurrence is low are likely to derive little overall benefit from the use of adjuvant systemic therapy, whereas those with a high risk of recurrence are likely to receive the greatest benefit. Regardless, comorbidities must always be considered on an individual basis.

Table 38.6 Effect of Systemic Therapy on Recurrence and Survival from Breast Cancer

Age	Therapy	Reduction in Annual Odds of Recurrence	Reduction in Annual Odds of Death
<50	Tamoxifen × 5 yrs	45 ± 8	32 ± 10
50–59	Tamoxifen × 5 yrs	37 ± 6	11 ± 8
60–69	Tamoxifen × 5 yrs	54 ± 5	33 ± 6
<40	Polychemotherapy	37 ± 7	27 ± 8
40–49	Polychemotherapy	35 ± 5	27 ± 5
50–59	Polychemotherapy	22 ± 4	14 ± 4
60–69	Polychemotherapy	18 ± 4	8 ± 4

From **Early Breast Cancer Trialists' Collaborative Group**. Polychemotherapy for early breast cancer: an overview of the randomized trials. *Lancet* 1998; 352: 930, with permission.

The current recommendations for adjuvant systemic therapy in breast cancer are summarized as follows:

- Premenopausal women with lymph node involvement should be treated with adjuvant combination chemotherapy. *Tamoxifen* should be added for patients with estrogen receptor–positive tumors following cytotoxic therapy.
- Premenopausal women without evidence of axillary lymph node involvement but with large (>1 cm) size, aneuploid, or estrogen receptor–negative tumors should be treated with combination chemotherapy. *Tamoxifen* should be given to patients with estrogen receptor–positive tumors.
- Postmenopausal patients with negative lymph nodes who are hormone receptor positive should receive adjuvant *tamoxifen* or aromatase inhibitor therapy. Those with positive lymph nodes may receive *tamoxifen* or an aromatase inhibitor alone, multidrug cytotoxic therapy, or a combination thereof.
- Postmenopausal women with lymph node metastases who are hormone receptor negative may be treated with adjuvant chemotherapy.
- Adjuvant systemic therapy is not recommended for patients with favorable tumors smaller than 1 cm. Hormonal therapy may be considered if the patient is estrogen receptor positive.

Prognosis

The treatment of advanced, metastatic breast cancer is largely palliative. For most physicians, quality-of-life issues are paramount when choosing which type of therapy is

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offered. In patients with locally advanced disease in conjunction with distant metastasis, palliative radiotherapy may be advised to control pain or avoid pathologic fractures. This approach is best exemplified in the treatment of isolated bone metastases, chest wall recurrences, brain metastases, and spinal cord compression.

Systemic disease may be controlled by hormonal or cytotoxic therapy. Because the quality of life during an endocrine-induced remission is usually superior to one following cytotoxic chemotherapy, it is preferable to try endocrine manipulation first. As many as one third of patients with disseminated disease respond favorably to either functional end-organ ablation (ovary, pituitary, adrenal glands) or administration of drugs that block hormonal function. For patients with estrogen receptor–positive tumors, this response rate may be as high as 60%. Because only 5% to 10% of women with estrogen receptor–negative cancers respond to endocrine treatment, they should not routinely receive hormonal therapy except in unusual cases, such as elderly women who are intolerant of cytotoxic therapy (107).

Cytotoxic chemotherapy should be considered for the treatment of metastatic breast cancer if organ involvement is potentially life-threatening (brain, lung, or liver), if hormonal treatment is unsuccessful, if the disease has progressed after an initial response to endocrine manipulation, or if the tumor is estrogen receptor negative. The most useful single chemotherapeutic agent is an anthracycline such as *doxorubicin*, which has an estimated response rate of 40% to 50%. Combination therapy using multiple agents has response rates as high as 60% to 80% (108). Clinical trials, including those investigating the use of *Herceptin* for Her-2/*neu*-positive women with metastases, are under way to examine a variety of combinations for stage IV disease. The historically prominent side effects of debilitating nausea and vomiting are now well controlled with central-acting antiemetics. The importance of controlling these potentially devastating symptoms cannot be overemphasized.

Special Breast Cancers

Paget Disease

In the 1870s, Sir James Paget first described a nipple lesion similar to eczema and recognized that this nipple change was associated with an underlying breast malignancy (109). The erosion results from invasion of the nipple and surrounding areola by characteristic large cells with irregular nuclei, now called Paget cells. Although the origin of these cells has been much debated by pathologists, they are probably extensions of an underlying carcinoma into the major ducts of the nipple–areolar complex. There may be no visible changes associated with the initial invasion of the nipple. Often, the patient's presenting symptom will be nipple discharge, which is actually a combination of serum and blood from the involved ducts.

The overall prognosis for patients with this rare form of breast cancer depends on the stage of the underlying malignancy. When an intraductal carcinoma alone is identified, the prognosis remains favorable, whereas patients with infiltrating ductal carcinoma metastatic to the regional lymph nodes have worse outcomes. Traditionally, treatment has almost always been total mastectomy and lymph node dissection, although breast conservation therapy with resection of the tumor and nipple–areolar complex, followed by whole breast radiation, is being performed in appropriately identified patients (110).

Inflammatory Carcinoma

Patients presenting with inflammatory carcinoma initially appear to have acute inflammation of the breast with corresponding redness and edema. Additional clinical findings are variable and range from complete absence of a dominant mass to the presence of either satellite skin nodules or a large palpable abnormality.

Inflammatory cancer, rather than infiltrating ductal carcinoma, should be diagnosed when more than one third of the breast is involved with erythema and edema and when biopsy of the involved area, including the skin, demonstrates metastatic cancer in the subdermal lymphatics. Most of these tumors are poorly differentiated. Mammographically, the breast shows skin thickening with an infiltrative process and may or may not identify a mass or calcifications.

Except for biopsy of the lesion to establish the diagnosis, surgery is not part of the initial management of inflammatory carcinoma. Mastectomy usually fails locally within 2 years of the initial diagnosis and does not improve overall or disease-free survival rates. **Better results are achieved with a combination of chemotherapy and radiation therapy.** Mastectomy may be indicated for patients who remain free of distant metastatic disease after initial chemotherapy and radiation (111).

In Situ Carcinomas

Both lobular and ductal carcinoma may be confined by the basement membrane of the ducts. These carcinomas do not invade the surrounding tissue and, theoretically, lack the ability to spread.

Lobular Carcinoma In Situ

***Lobular carcinoma in situ* should not be considered a true malignancy but rather a risk factor for the subsequent development of invasive ductal or lobular carcinoma in either breast (112).** A more appropriate nomenclature for lobular carcinoma *in situ* may be lobular neoplasia. Most women with lobular carcinoma *in situ* are premenopausal and have neither clinical nor mammographic signs of an abnormality. The lesion typically is not a discrete mass, but rather a multifocal entity within one or both breasts incidentally discovered by the pathologist during the evaluation of a completely unrelated issue. Lobular carcinoma *in situ* usually is managed with an excisional biopsy followed by careful surveillance with clinical breast examinations and mammography. Occasionally, a patient may request either bilateral prophylactic mastectomy or *tamoxifen* for chemoprevention. **Women with lobular carcinoma *in situ* have a 1% per year and up to a 30% lifetime risk of developing an invasive cancer.**

Ductal Carcinoma In Situ

Ductal carcinoma *in situ* is more common in postmenopausal women. It may manifest as a palpable mass but usually is detected mammographically as a cluster of branched or Y-shaped pleomorphic microcalcifications. By definition, intraductal disease does not invade beyond the basement membrane. **Unlike patients with lobular carcinoma *in situ*, 30% to 50% of patients with ductal carcinoma *in situ* will develop an invasive ductal cancer within the same breast if treated by excisional biopsy alone (113).**

Although modified radical mastectomy was previously the standard treatment for intraductal carcinoma, more conservative surgery, with or without radiation therapy, has been shown to yield good results. In NSABP trial B17, 818 patients were randomly assigned to excision alone or excision followed by radiation therapy. The mean extent of ductal carcinoma *in situ* lesions was 13 mm, and 88% were larger than 20 mm. All lesions were completely resected with negative margins. After a median follow-up of 43 months, the actuarial 5-year local recurrence rate was 10.4% without radiation versus 7.5% with radiation ($P = 0.055$) for noninvasive cancers, and 10.5% without radiation versus 2.9% with radiation ($P > 0.001$) for invasive cancers. Of 83 recurrences, only 9 (11%) were not in the index quadrant. A recent reanalysis with a mean follow up of 90 months confirmed these results (114). **These data suggest that segmental mastectomy offers excellent local control.**

Axillary metastases occur in fewer than 5% of patients diagnosed with ductal carcinoma *in situ*, making routine axillary dissection unnecessary. When axillary disease is

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identified, further evaluation of the breast or surgical specimen or both is warranted because nodal metastases indicate that an invasive ductal component was missed. Sentinel node biopsy may be offered to certain individuals with ductal carcinoma *in situ*, especially if the lesion is high grade, contains comedonecrosis, or was diagnosed on core biopsy and has clinical or radiographic features suggesting invasive disease. About 5% of patients whose initial biopsy results show intraductal carcinoma will be found to have infiltrating ductal carcinoma when treated with mastectomy, whereas core biopsy may underestimate the invasiveness of the disease in up to 20% of patients. The incidence of contralateral breast cancer in women with intraductal carcinoma is the same as in those with invasive ductal carcinoma (5%–8%) (115).

Breast Cancer in Pregnancy

Breast cancer complicates 1 in 3,000 pregnancies (116,117). It is the second most common malignancy seen in association with pregnancy, surpassed only by cervical cancer (118). Initial studies suggested a significantly worse prognosis for patients first diagnosed during pregnancy, but recent data indicate that the hormonal changes associated with pregnancy seem to have little, if any, influence on prognosis. **When pregnant patients are matched stage for stage with nonpregnant patients, survival rates seem equivalent** (119). Patients typically present with a painless mass. Up to 60% will have concurrent lymph node involvement. The evaluation includes imaging with ultrasonography and mammography, which, although controversial, expose the fetus to less than 0.02 cGy of radiation and may be obtained with proper abdominal shielding (120). If biopsy is warranted, the procedure can be performed safely and should not be delayed until after delivery. Needle biopsy is safe and easily accomplished in the office setting.

The treatment of breast cancer in pregnant women must be highly individualized. Considerations include the patient's age and desire to continue the pregnancy. The overall prognosis should be considered, especially when axillary lymph nodes are involved, because adjuvant chemotherapy can be teratogenic or lethal to the fetus during the first trimester, but may be given later in the pregnancy. It is believed that interruption of pregnancy does not alter the prognosis for patients with potentially curable breast cancer.

Following are generalized recommendations for treatment of pregnant women with breast cancer:

- **Traditionally, cancers diagnosed during the first or second trimester of pregnancy have been treated with modified radical mastectomy. Sentinel node biopsy remains a controversial procedure in pregnancy;** the use of blue dye is contraindicated, and the safety of radiocolloid has not been documented. In addition, most centers do not offer breast conservation therapy based on the theory that radiation therapy should not be given to the gravid patient. In a patient diagnosed before the third trimester, waiting until after delivery may result in an unacceptable delay in the initiation of therapy and should not be encouraged. Adjuvant chemotherapy can be given after the first trimester, although many oncologists prefer not to give it to pregnant women outside of clinical trials. A classic study reported the risk of fetal malformations to be 20% during the first trimester, a rate which dropped to 1.5% during the second and third trimesters (121). *Tamoxifen*, however, is a class D drug and should not be given to pregnant or lactating patients with breast cancer.

- **Localized tumors found during the third trimester of pregnancy can be managed**

with breast conservation therapy, with radiation delayed until after delivery, or with modified radical mastectomy. Initially, tumors should

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be excised early in the third trimester using local anesthesia. If delivery is imminent, standard therapy can be performed immediately postpartum. In the patient with a viable fetus, it may be preferable to induce early labor to avoid delaying definitive cancer therapy.

- **If the breast cancer is diagnosed during lactation, lactation should be suppressed and the cancer should be treated definitively.**

- **Advanced, incurable cancer should be treated with palliative therapy.** Decisions regarding continuation of the pregnancy should be based on the therapy necessary and the desires of the mother.

Counseling regarding future childbearing is important for women who have had carcinoma of the breast. Although it generally has been assumed that subsequent pregnancies are detrimental because of the high levels of circulating estrogens, **there is no clear difference in survival for women who become pregnant after the diagnosis of breast cancer.** One study evaluated the effect of subsequent pregnancy on overall survival after the diagnosis of early-stage breast cancer. Although approximately 40% of the women in the study had node-positive disease, 5- and 10-year survival rates were better in women who became pregnant than in matched pair controls who did not. This study suggests that subsequent pregnancy does not adversely affect the prognosis of early-stage breast cancer (122). A subsequent investigation demonstrated no increase in the relative risk of death for patients who gave birth more than 10 months after their initial diagnosis of cancer (123). Theoretically, it may be that only women with estrogen receptor-positive or progesterone-positive tumors would be affected deleteriously by subsequent pregnancy, but this possibility has not been studied. Because recurrences are most frequent within the first 2 to 3 years after diagnosis, patients with receptor-positive tumors and advanced-stage disease probably should wait until after that time before becoming pregnant again.

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